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UNIVERSITY OF ALBERTA

Biosynthetic and Synthetic Studies on Polyketides: Biomimetic Polyketide Models and Lovastatin

BY

David James Witter

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Fall 1994

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Date: MAY 17, 1994

To my wife, Cathy, and daughter, Nicole

Abstract

The biosynthesis of lovastatin (**5**) (formerly mevinolin) by *Aspergillus terreus* MF 4845 was examined by feeding experiments using the *N*-acetylcysteamine (NAC) thioester of [2,11-$^{13}C_2$]-(*E*,*E*,*E*)-(*R*)-6-methyldodecatri-2,8,10-enoate (**50a**). The synthesis of this triene precursor incorporated the two ^{13}C labels in the late stages of construction using both Wittig olefination chemistry and the Schlosser modification of the Wittig reaction. *In vitro* cyclization of unlabeled triene NAC ester **50**, its ethyl ester **83** and its free-acid **85** yielded the two analogous diastereomers in each case, under either thermal or Lewis acid catalyzed conditions. In the case of triene ethyl ester **83**, the absolute structure of one diastereomer was deduced by 1D and 2D NMR techniques to be *trans*-fused ethyl (1*R*, 2*R*, 4a*S*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethyl-naphthalen-1-carboxylate (**92**). A reference compound with the same bicyclic stereochemistry as lovastatin (**5**) was constructed by derivatization of a known tricyclic lactone, (1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1-(ethoxycarbonyl)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-6,8-naphthalenecarbolactone (**108**), using reduction and Barton deoxygenation techniques to give ethyl (1*S*, 2*S*, 4a*R*, 6*R*, 8a*S*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylate (**93**). Comparison of **93** with the ethyl esters of the two diastereomers obtained from the Diels-Alder cyclization of **83** illustrated that the two non-enzymatic Diels-Alder products possessed a different bicyclic stereochemistry than that of lovastatin. Using nOe NMR techniques, the structure of the second ethyl ester diastereomer was confirmed as *cis*-fused ethyl (1*R*, 2*S*, 4a*R*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethyl-naphthalen-1-carboxylate (**94**).

Successful intact incorporation of the labeled hexaketide (**50a**) was not achieved, possibly due to transport difficulties. The labeled precursor was not able to

penetrate the fungal cell wall before being degraded or before intramolecular cyclization to undesirable materials occurred.

Model systems to mimic the *in vivo* assembly of polyketides were explored using two independent templates. 2-Hydroxybenzyl alcohol (**13**) functionalized with an acetate and a malonate on the benzylic and phenolic hydroxyl groups respectively, proved to be too unstable due to the possible generation of a highly reactive intermediate species, 6-methylene-2,4-cyclohexadien-1-one (**18**). It was also shown that selectively acylated derivatives of 8-hydroxy-1-naphthalenemethanol (**23**) when treated with lithium hexamethyldisilazane resulted in intermolecular condensation reactions, instead of the desired intramolecular processes.

Acknowledgements

I would like to thank my supervisor, Professor John C. Vederas, for his guidance and motivation during my studies. I would also like to thank Dr. Yuko Yoshizawa for her contribution to this thesis. I am grateful to Dr. Russell J. Cox and Dr. Chris Lowe for their help and proof-reading of this manuscript. The assistance of Dr. T. Mark Zabriskie in running NMR spectra is also appreciated. My thanks are extended to the staff of spectral and analytical services for their assistance in characterizing compounds.

The Natural Sciences and Engineering Research Council of Canada, and the University of Alberta are gratefully acknowledged for financial support. Finally, I would like to thank my wife, Cathy, for her unfailing support and encouragement.

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List of Abbreviations

Ac	acetyl
ACP	acyl carrier protein
AIBN	α,α'-azobis(isobutyronitrile)
AT	acyltransferase
ax	axial substituent
bp	boiling point
Bu	butyl
n-BuLi	*n*-butyl lithium
CI	chemical ionization
CoA	coenzyme A
COSY	correlated spectroscopy
d	doublet
DAST	diethylaminosulphur trifluoride
DCC	1,3-dicyclohexylcarbodiimide
DH	dehydratase
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4,4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact ionization
Enz	enzyme
eq	equatorial substituent
ER	enoylreductase
Et	ethyl

FAB	fast atom bombardment
FAS	fatty acid synthase
FID	flame ionization detector
GC	gas chromatography
h	hour
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
IR	infrared
KR	ketoreductase
KS	ketoacyl synthase
LCFA	long chain fatty acid
LDL	low-density lipoprotein
LHMDS	lithium hexamethyldisilazane
m	multiplet
Me	methyl
min	minute
MOM	methoxymethyl
mp	melting point
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
NAC	*N*-acetylcysteamine
NADPH	nicotinamide adenine dinucleotide phosphate, reduced form
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
ORF	open reading frame
OSA	orsellinic acid synthase

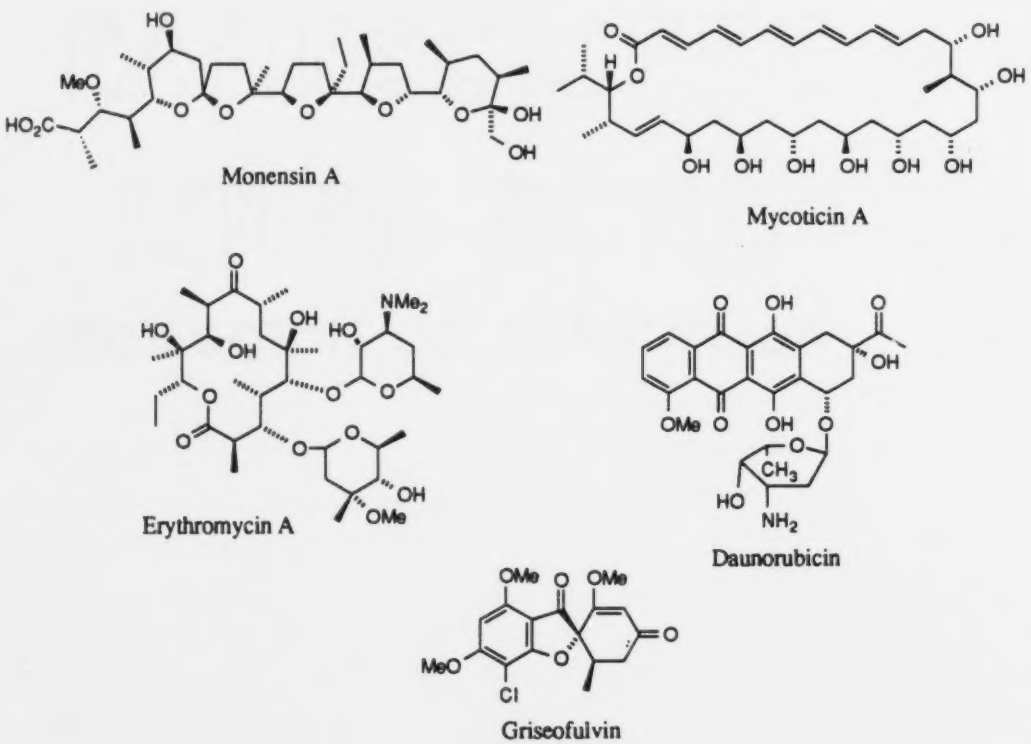
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PKS	polyketide synthase
Pr	propyl
q	quartet
R_f	retention factor
RP	reverse phase
s	singlet
sec	second
SU	synthase unit
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	*p*-toluenesulfonyl

INTRODUCTION

BIOSYNTHETIC FORMATION OF POLYKETIDES

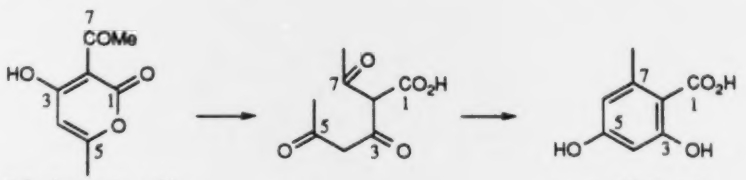
Polyketides form a vast family of natural products, most of which are produced by bacteria and by fungi. They have such structural diversity that superficial examination reveals no obvious interrelation, but insights from biosynthetic experiments show them to be derived from successive condensations of small carboxylic acids.[1] They include many commercially interesting compounds such as the macrolide (e.g. erythromycin A), polyether (e.g. monensin A) and polyene (e.g. mycoticin A) antibiotics, and the polyaromatic antitumor (e.g. daunorubicin) and antifungal (e.g. griseofulvin) agents depicted in Figure 1.

Figure 1. Structures of polyketide metabolites

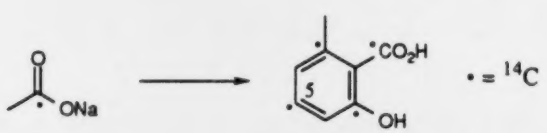


The now accepted hypothesis of polyketide biosynthesis was first alluded to by Collie in 1907.[2] Experimentally, Collie showed that dehydroacetic acid, itself derived from two molecules of acetoacetate, rearranged under basic conditions to give orsellinic acid (Scheme 1). He extrapolated that biological systems could act in a similar fashion to this laboratory process.

Scheme 1.



Birch extended this conjecture by postulating that these natural products were formed through successive head-to-tail linkages of acetate units.[3] He provided the first biological support for this hypothesis through the observation of incorporation of ^{14}C-acetate into the predicted positions of 6-methylsalicylic acid.[4]

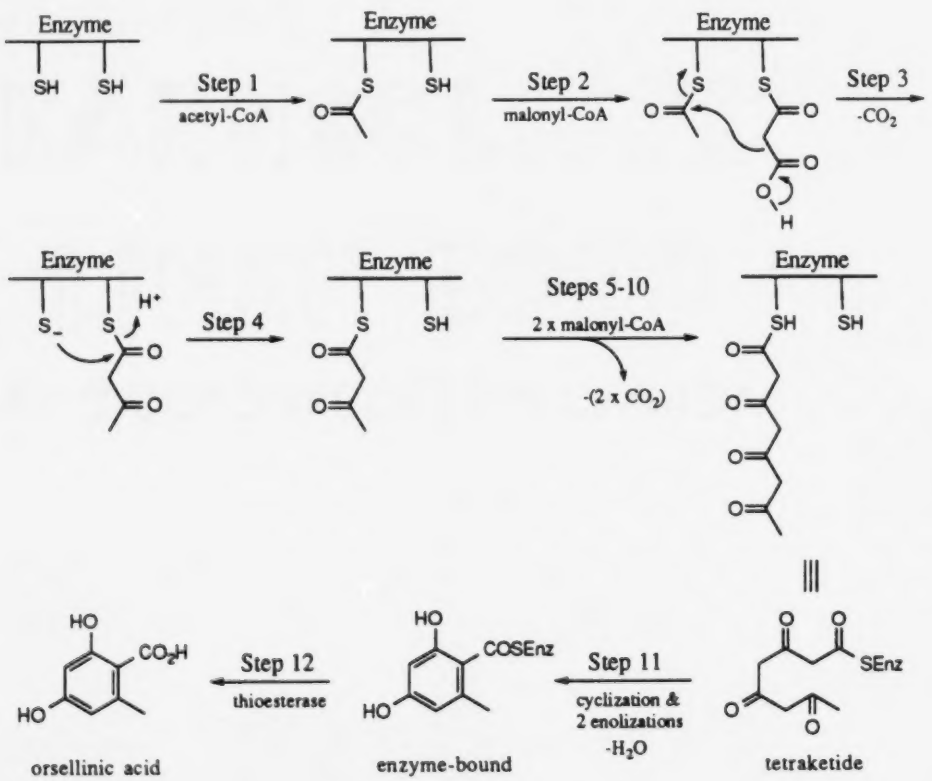


6-methylsalicylic acid

A comparison between the biosyntheses of two of the simplest polyketides, orsellinic acid and 6-methylsalicylic acid, illustrates the head-to-tail linkages of constituent acetate units, and how the functionality of the polyketide chain can be modified as it is extended by the polyketide synthase (PKS). Orsellinic acid is structurally very similar to 6-methylsalicylic acid, except for the presence of an extra hydroxyl group at C-5 in the former. Its biosynthesis has been investigated using orsellinic acid synthase (OSA) isolated from orsellinic acid producing strains of *Penicillium cyclopium* and *Penicillium madriti*.[5] It was found that orsellinic acid could

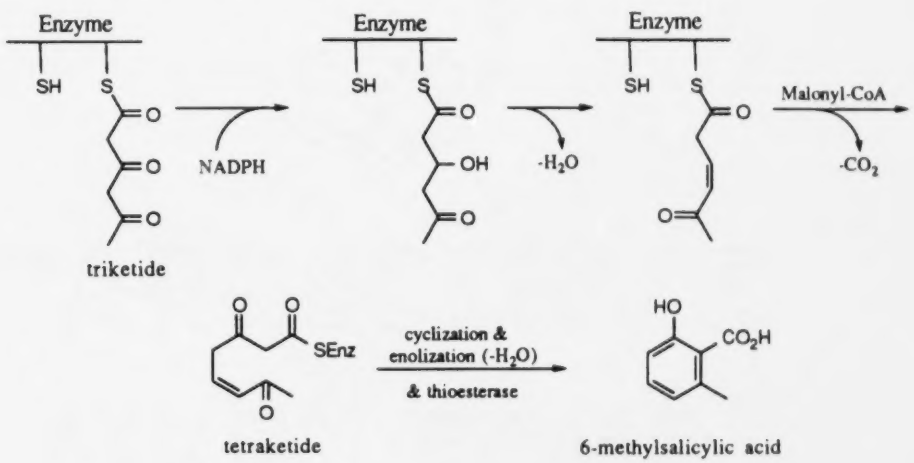
be synthesized in a cell-free system containing the OSA suspended in an aqueous buffer in the presence of only acetyl-CoA and malonyl-CoA (Figure 2). The process begins with the trans thio-esterification of acetyl-CoA and malonyl-CoA onto thiols contained within the active site (steps 1 & 2, Figure 2). Decarboxylative condensation (step 3) leads to a β-keto thioester, which is transesterified to the original thiol (step 4). The cycle of condensation and decarboxylation occurs two more times affording a tri-keto thioester (tetraketide). A Claisen condensation followed by two enolizations (step 11) generates enzyme bound orsellinic acid which is then released (step 12) by a thioesterase. This process resembles that of fatty acid biosynthesis by fatty acid synthase (FAS); however FAS fully reduces the β-keto functionality before the next round of extension by malonate.[6]

Figure 2. Biosynthesis of orsellinic acid



In contrast to orsellinic acid, the biosynthesis of 6-methylsalicylic acid from an acetate starter unit and three molecules of malonyl-CoA requires the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH).[7] Its formation parallels that of orsellinic acid in that the polyketide chain is extended to the tetraketide before cyclization occurs, but is more complex due to reduction by NADPH and subsequent dehydration of the resultant β-hydroxy functionality after the second cycle of chain extension. The biosynthesis from the triketide, shown in Figure 3, illustrates that the growing polyketide chain can be modified before a two carbon chain extension is performed.

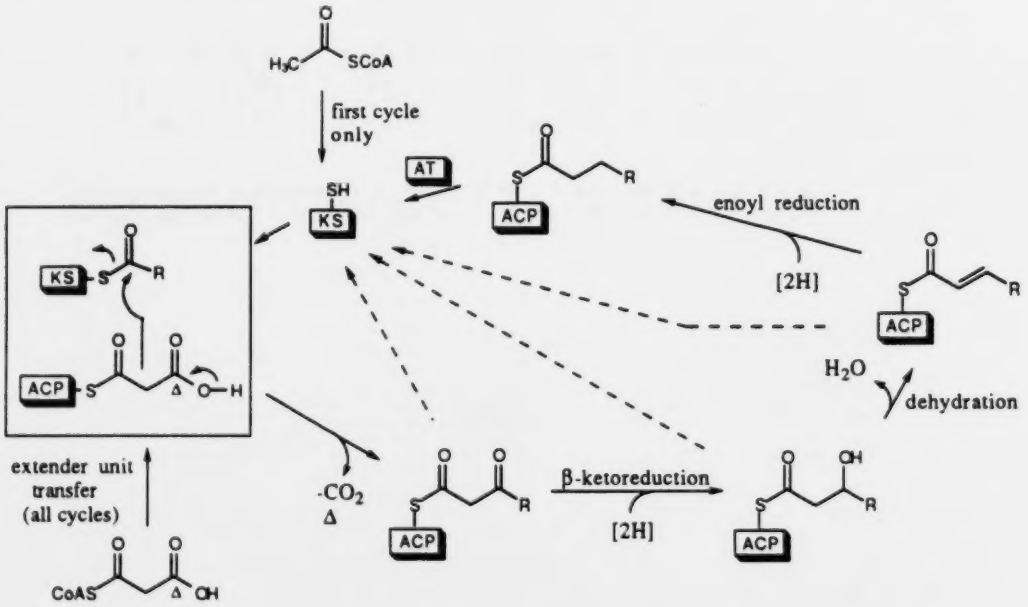
Figure 3. Biosynthesis of 6-methylsalicylic acid from the triketide



This kind of process adequately explains the construction of many aromatic polyketides, but the formation of more reduced examples, the complex polyketides (e.g. monensin, etc.), poses many questions, especially about the regioselectivity of the functionalizations. Initially it was postulated that long poly-β-keto structures were generated, which were then modified in subsequent steps.[3b] The currently accepted hypothesis suggests that a substantial analogy exists between the formation of polyketides by polyketide synthases (PKS) and synthesis of long chain fatty acids (LCFA) by fatty acid synthases (FAS). Generally the construction of fatty acids begins with the starter

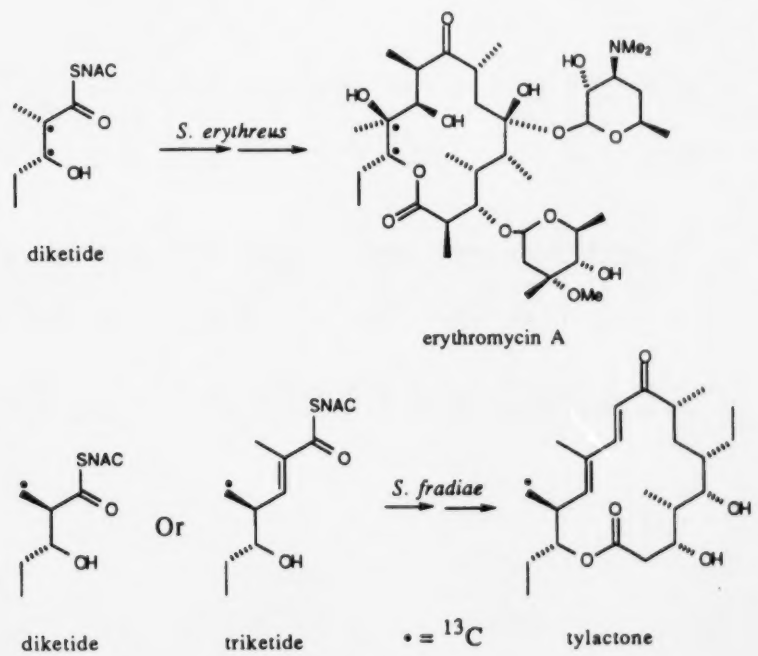
acetyl group of acetyl-CoA being transferred to the active site thiol of the condensing enzyme, ketoacyl-ACP synthase (KS) (Figure 4).[6] The extender unit, malonate, is transferred from CoA (coenzyme A) to the pantotheine arm of the acyl carrier protein (ACP) by acyltransferase (AT). The acetate condenses with malonate with simultaneous loss of CO_2. In FAS, the cycle continues to fully reduce the β-ketone to a methylene unit as shown in Figure 4 (bold arrows) and the resultant extended acyl group reenters the cycle at the starting point. The intermediates remain enzyme bound during the process. The more highly programmed PKS differs from FAS in the following aspects: 1) a larger range of starter units are possible (e.g. linear and branched carboxylic acids, etc); 2) more extender units can be used (e.g. malonyl-CoA, methylmalonyl-CoA, or ethylmalonyl-CoA); and 3) the β-ketone functionality can retain different oxidation states by skipping some subsequent modifications. The extended chain can enter a new cycle containing a β-keto, β-hydroxy, α,β-unsaturated, or fully reduced β-carbon. After the required number of cycles, the chain is released by acyl transfer or thiolysis, and is then subsequently transformed to the final metabolite by post-PKS reactions.

Figure 4. Fatty acid and polyketide biosynthesis



Current research on complex polyketides supports this processive mechanism in which reduction at the β-position occurs before the condensation of the next C_2 unit. Cane and Yang[8] and Yue *et al.*[9] showed that *N*-acetylcysteamine derivatives of suitable precursor compounds with the stereochemistry of putative intermediates in the biosynthetic pathway of erythromycin and tylactone (the aglycone of tylosin), respectively, were incorporated into each metabolite (Figure 5). These were the first demonstrations of intact incorporations of polyketide intermediates into the macrolide antibiotics; that is, the precursors were not degraded by oxidative enzymes prior to their utilization by the PKS systems. The *N*-acetylcysteamine (NAC) thioester moiety is essential for intact incorporation, and is believed to mimic the acyl-ACP ester in the active site of the polyketide synthase.[9]

Figure 5. Incorporations of putative intermediates into erythromycin and tylactone



This approach has also been applied successfully to fungal systems using acetate-derived precursors. Intact utilization of di- and tetraketide intermediates in

dehydrocurvularin was achieved through the use of blocked mutants[10] or inhibitors of β-oxidation (Figure 6).[11] Incorporations of acetate and propionate-derived polyketide intermediates have also been observed in actinomycete and other fungal metabolites, nargenicin,[12,8b] nonactin, [13] aspyrone,[14] methymycin,[15] monensin A,[16] and tetronasin (Figure 6).[17] In each case, the synthetic precursors, possessing the stereochemistry of proposed biosynthetic intermediates formed after one, two, or more cycles of the PKS, are accepted by the PKS, and are subsequently transformed to the final product. These studies support the stepwise processive mechanism.

Isolation of new compounds generated from mutant polyketide-producing strains provides additional evidence for this pathway.[18,19] Mutants which lack the ability to produce a biosynthetically important enzyme may be blocked in production of the final metabolite and accumulation of preceding intermediates may occur in sufficient quantities to be isolated and identified. A series of branched acids were isolated during mutagenic studies on *Micromonospora griseorubida*, the producer of mycinamycin (Figure 7).[18]

Figure 7. Accumulated intermediates for metabolites protomycinolide and tylactone

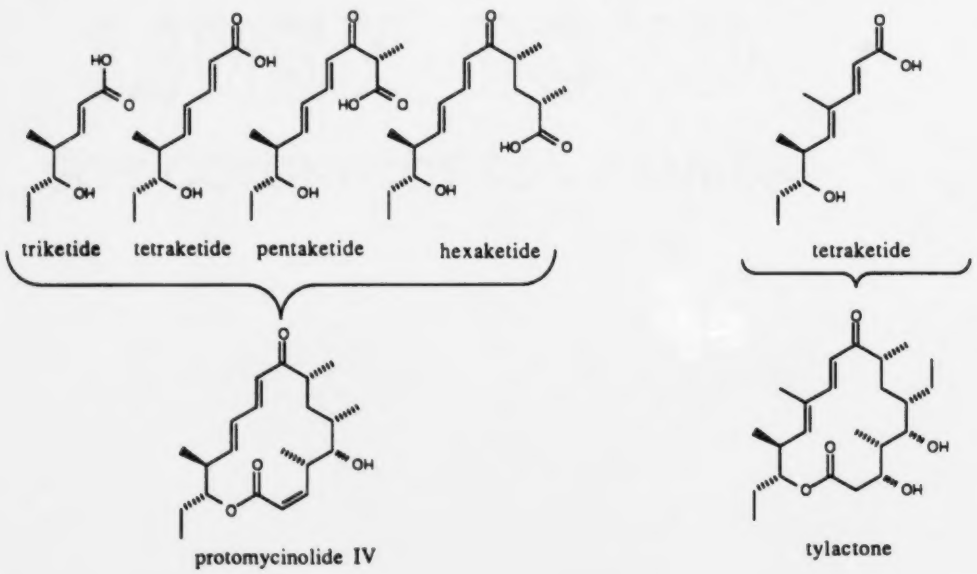
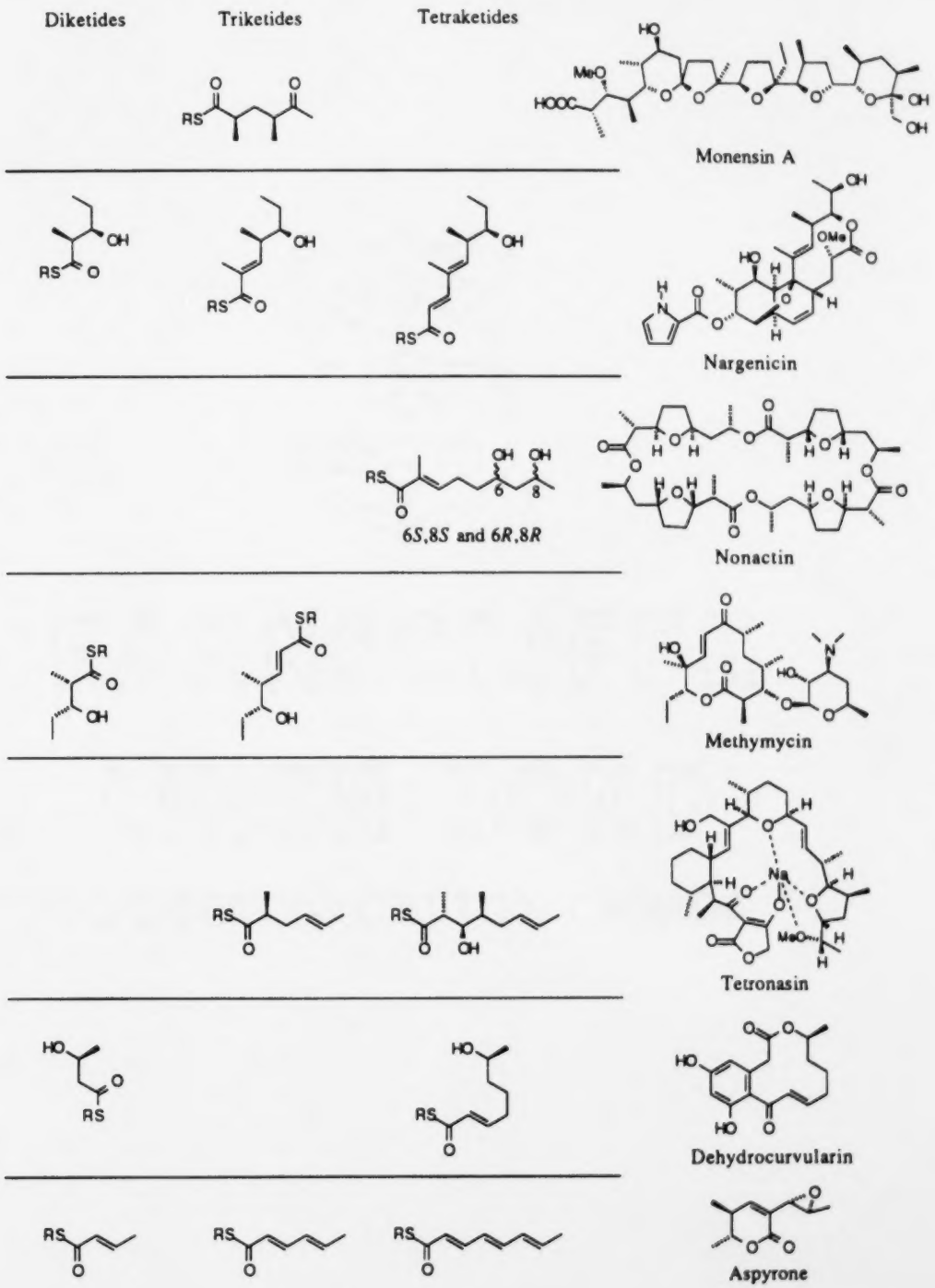


Figure 6. Intermediates incorporated into various polyketides. The isotopic labeling and thioester structure are not shown for simplicity.

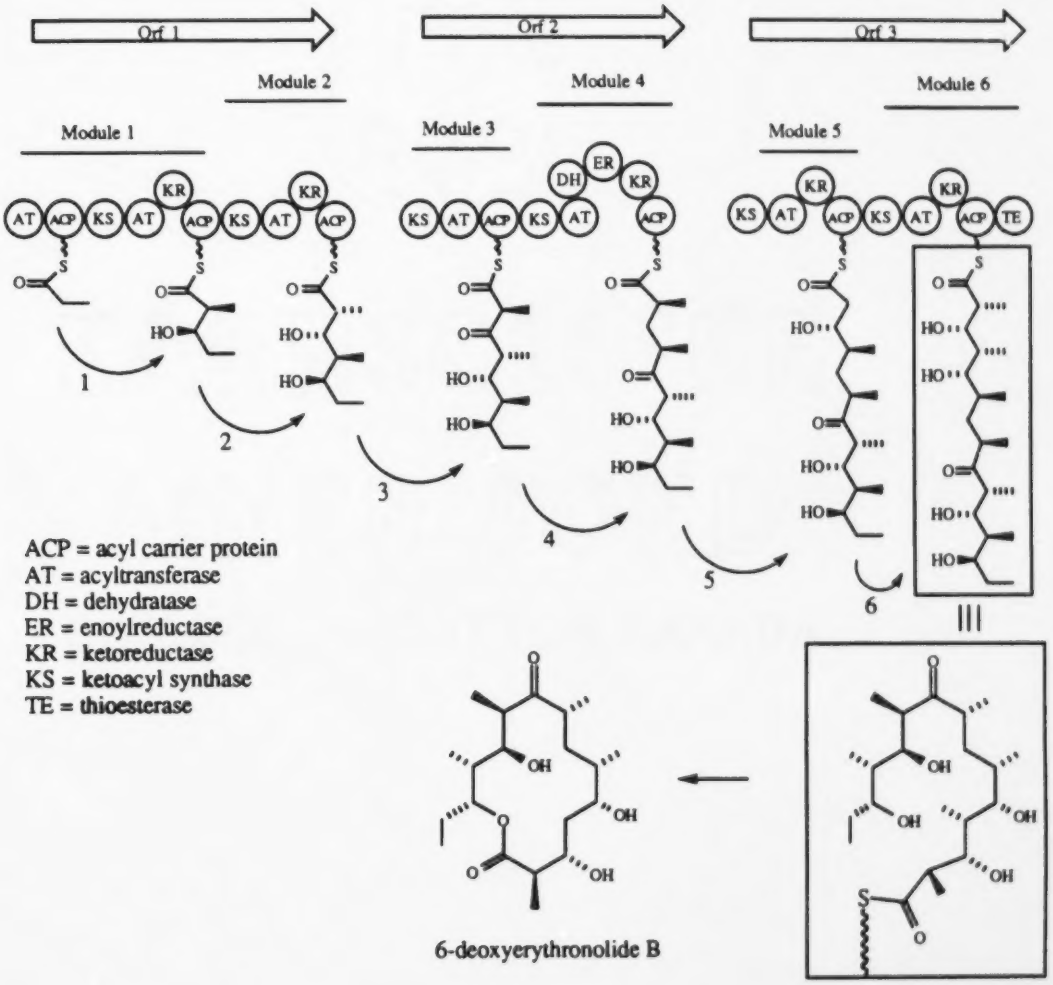


The isolated tri- to hexaketides have structures and stereochemistry corresponding to polyketide intermediates expected during the construction of the mycinamycin aglycone, protomycinolide IV. In another example, a mutant strain of the tylosin producer, *Streptomyces fradiae*, produces a tetraketide (Figure 7).[19] This compound corresponds to a putative intermediate in the biosynthesis of tylactone, the aglycone of tylosin.

The application of molecular genetics to polyketide biosynthesis provides valuable insight into the organization and function of the PKS for the formation of polycyclic aromatic and complex natural products.[20] During each cycle the enzymatic assembly system seems to control three important features: 1) the type of extender units to incorporate (e.g. malonyl-CoA, methylmalonyl-CoA, or ethylmalonyl-CoA); 2) the extent of processing to be performed on the newly formed β-keto moiety; and 3) the stereochemical outcome of these transformations. Recently Katz[21] and Leadlay,[22a] have independently cloned and sequenced the genes from *Saccharopolyspora erythraea* responsible for the biosynthesis of the erythromycin aglycone, 6-deoxyerythronolide B. This polyketide is formed from the head-to-tail condensation of a propionyl-CoA starter unit and six methylmalonyl-CoA extender units. The *eryA* gene encodes for a large multifunctional polypeptide containing putative FAS-like activities (Figure 8). The gene is comprised of 3 ORFs (open reading frames) each of which consists of two repeating units called modules; the corresponding protein segments are called synthase units (SU). Each module contains the sequences needed for coding the appropriate complement of the ketosynthase (KS), ketoreductase (KR), dehydratase (DH), enoylreductase (ER), acyl carrier protein (ACP), and acyltransferase (AT) domains, which show remarkable amino acid sequence homology to those found in fatty acid synthase. The synthase unit has been proposed to be responsible for the determination of the correct starter unit, the condensation reaction, and the extent of the processing that the β-carbon undergoes by virtue of the presence or absence of the appropiate functional domains.[22b,22c] For example, after the first condensation, the β-keto functionality is reduced to an alcohol by

KR (step 1, Figure 8). The alcohol is preserved as there are no DH or ER domains present before the next condensation. During step 4, the β-keto is fully reduced to a methylene as KR, DH, and ER are all present. The extended chain is then passed *via* the ACP to the KS of the next SU; the subsequent transformations are performed according to this SU and the cycle continues until the 6-deoxyerythronolide B is released by a thioesterase or putative cyclase (Figure 8).

Figure 8. Erythromycin polyketide synthase system

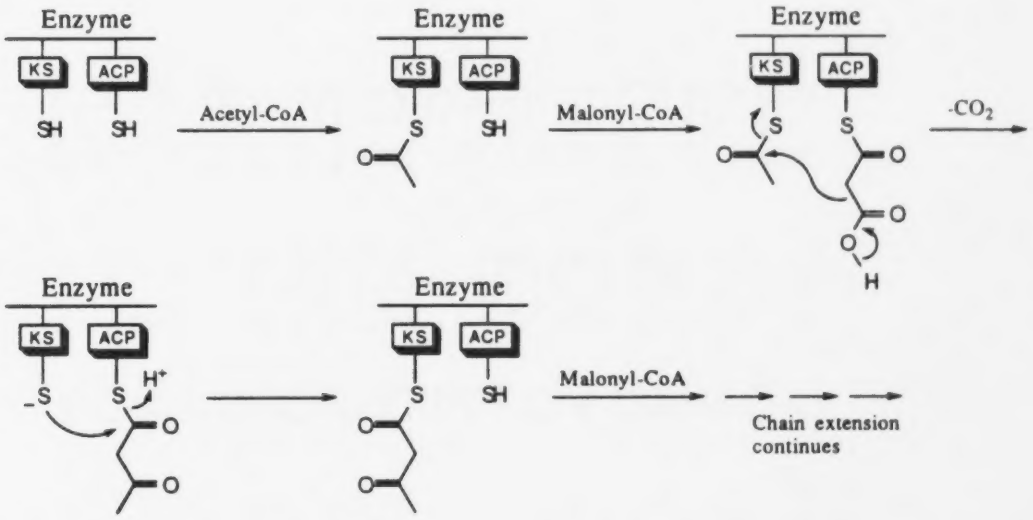


Very recently, progress has been made in the isolation of an unprecedented cell-free system capable of mediating the formation of complex aromatic or reduced polyketides from simple precursors.[23] A *Streptomyces* host-vector system allows for facile construction and expression of recombinant PKSs.[23b] Using this expression system several novel polyketide compounds have been synthesized *in vivo* in significant quantities. Further examination of the engineered biosynthesis should permit important insight into the fundamental aspects of metabolic control and molecular recognition of the PKS.

MODEL STUDIES OF POLYKETIDE BIOSYNTHESIS

As described in the previous section, a strong analogy exists between the formation of polyketides and long chain fatty acids, which proceed through a head-to-tail condensation of acyl units in a formal Claisen condensation. A simplified version of the first steps in polyketide formation involves attachment of a malonyl group to the acyl carrier protein and an acetyl group to the β-ketoacyl synthase, as thioesters. The carbon-carbon bond-forming reaction then occurs by an intramolecular decarboxylative condensation to deliver the β-ketothioester, which is subsequently transformed or extended further (Figure 9).

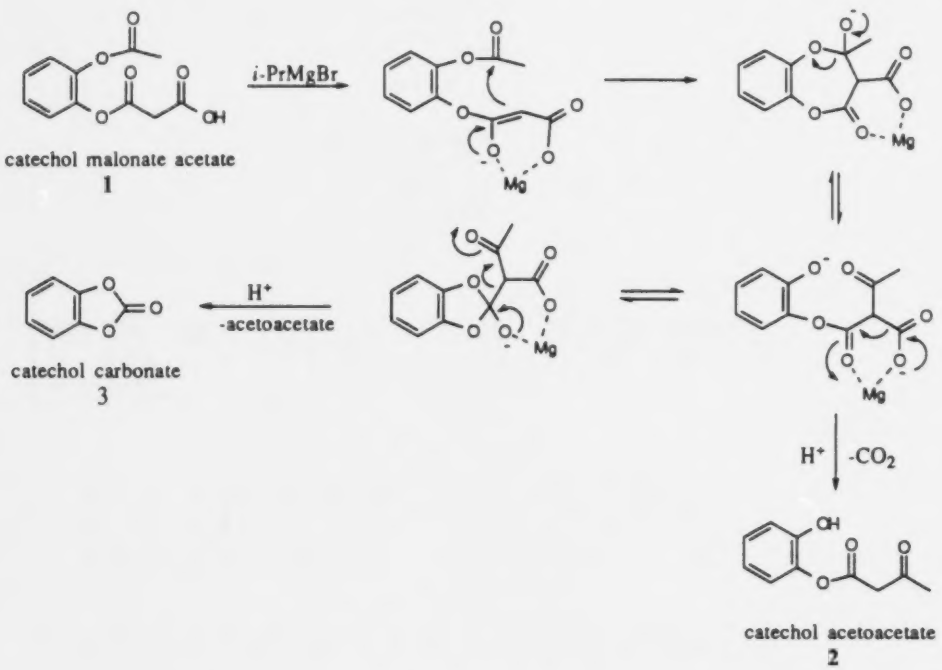
Figure 9. Initial steps of polyketide formation



Biomimetic studies on the initial reaction steps of polyketide formation have been reported.[24-26] The earliest example of acetyl transfer by Scott and coworkers used catechol as a template for the decarboxylative acylation by malonate on an acetyl starter unit (Scheme 2).[24] Catechol malonate acetate (**1**), upon treatment with two equivalents

of isopropyl magnesium bromide, produced the acetoacetate derivative of catechol in a low (30%) yield. The proposed pathway involves enolate formation of the malonate ligand and magnesium chelation, followed by condensation and decarboxylation. The other product formed in a 1:1 ratio with the acetoacetate **2** was catechol carbonate (**3**) arising from a rearrangement of the first condensation intermediate and loss of acetoacetate.

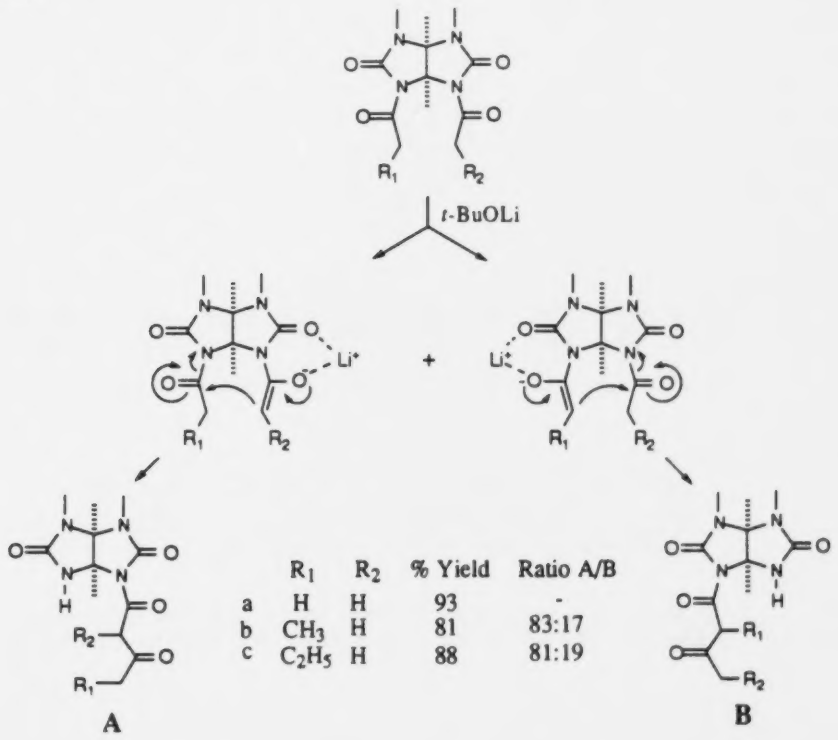
Scheme 2.



A second system achieved successful acetyl transfer with the *n*-butyl thioester of malonate and phenyl thioacetate in the presence of magnesium acetate and imidazole; however the transfer was intermolecular.[25] The desire for a higher yielding intramolecular acyl transfer reaction was pursued by a third model.[26] Recently Harrison used a bifunctional template where the acyl groups were attached on nitrogen atoms

(Scheme 3).[26] Rearrangement of the diacylated templates (a-c) proceeded after lithium *tert*-butoxide treatment to give the intramolecular acyl transfer products with reasonable regioselectivity in the asymmetric case (b and c) and in greater yields than in Scott's model. These results suggest a pathway involving a cyclic six-membered transition state with lithium chelation, since no *O*-acylated product was detected. The decarboxylative approach to enolate formation from a malonyl group in relation to this model, however, has not yet been reported.

Scheme 3.



	R_1	R_2	% Yield	Ratio A/B
a	H	H	93	-
b	CH_3	H	81	83:17
c	C_2H_5	H	88	81:19

We envisioned a biomimetic system that would encompass the positive aspects of these known models as well as including elements more consistent with the natural system. In polyketide synthase, the starter unit (usually acetate) is transferred to β-ketoacyl carrier protein and the extender unit (usually malonate) to the acyl carrier

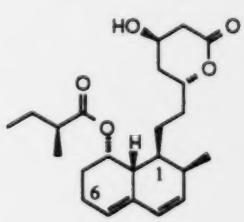
protein. The resultant β-ketoester condensation product remains bound to the acyl carrier protein during the subsequent reactions. After one cycle, the transformed acyl-ACP ester is transferred back to the condensing enzyme which orginally held the acetyl starter unit. Our aim was to test a bifunctional template having two different sites with one acting as the β-ketoacyl carrier protein and the second behaving as the acyl carrier protein, so that the resulting acetoacetate moiety could be returned to the original site of acetate attachment. The ketone in the acetoacetate could be protected, followed by malonylation to give a material capable of extending the protected polyketide chain; iterations of these steps might produce a long protected polyketide chain.

LOVASTATIN: DISCOVERY, MODE OF ACTION, AND BIOSYNTHESIS

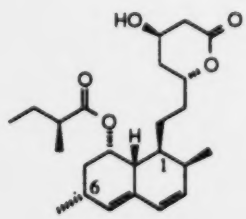
One class of microbial polyketides which are of intense current interest are agents which lower cholesterol levels in the bloodstream. Myocardial infarction is the major cause of death in Western industrialized countries.[27] Atherosclerosis, the progressive deposition of fibrotic material and lipids in the arterial wall, has been suggested as the primary cause of most infarctions.[27] It has been proposed that lowering the level of LDL (low-density lipoprotein) cholesterol in the bloodstream halts and reverses atherosclerosis[28] and lowers the incidence of coronary heart disease; thus an intensive search for drugs capable of regulating LDL levels has been undertaken.

In 1976, Endo *et al.* isolated a highly functionalized fungal metabolite, mevastatin (**4**) (ML-236B, CS-500, compactin), from *Penicillium citrinum*.[29] Researchers at Beecham Laboratories independently discovered this compound in *P. brevicompactum* (Figure 10).[30] This material reduces the level of plasma cholesterol after chronic administration in dogs[31] and monkeys.[32] After these initial reports on mevastatin were published, the efforts to discover new mevastatin analogues intensified. One of the most potent drugs, lovastatin (**5**) (mevinolin, monocolin K, Mevacor™), was isolated from *Aspergillus terreus* by Merck researchers[33] and was also independently isolated by Endo and coworkers from *Monascus ruber* (Figure 10).[34] Its structure is similar to that of mevastatin (**4**), with the exception of a 6α-methyl group in the hexahydronaphthalene ring.

Figure 10. Structures of mevastatin (**4**) and lovastatin (**5**)



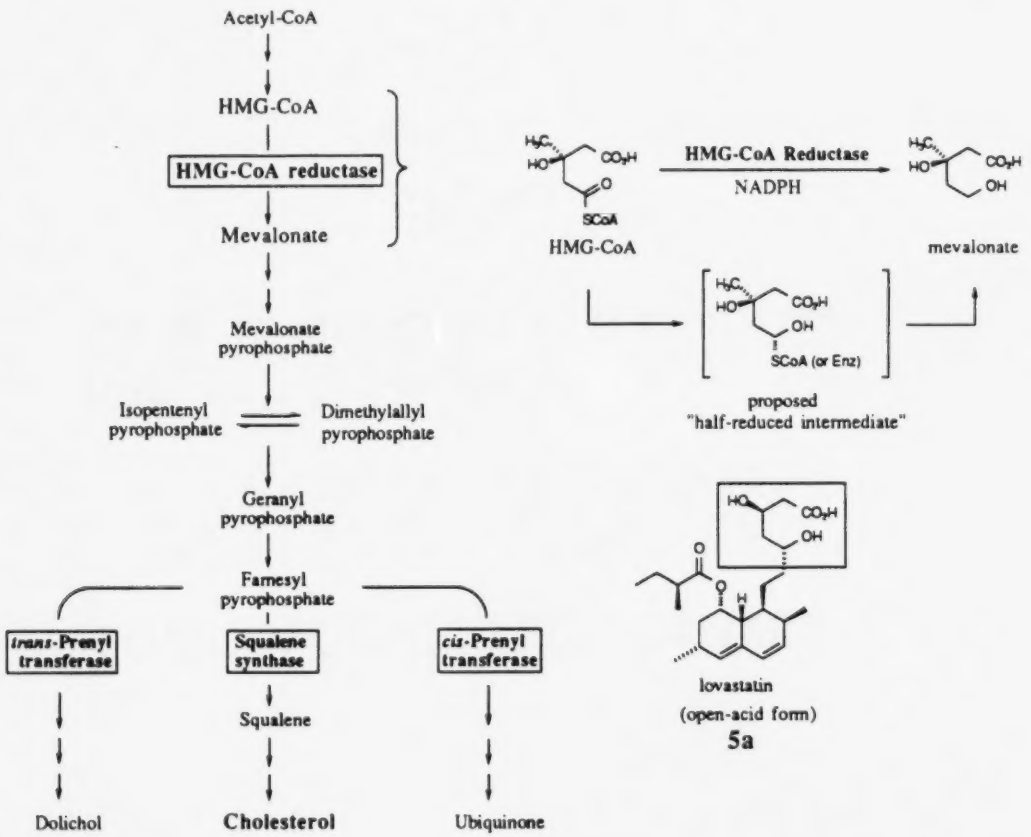
Mevastatin
4



Lovastatin
5

Lovastatin (**5**) and related drugs lower plasma cholesterol levels by the competitive reversible inhibition of the enzyme, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase.[35] Cholesterol, a vital component of eucaryotic membranes and a precursor of the steroid hormones and bile acids, is mainly synthesized in the liver from acetyl CoA.[36] The committed step in its synthesis is the transformation of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) to mevalonate by HMG-CoA reductase which uses NADPH in two independent reactions (Figure 11).[37]

Figure 11. HMG-CoA reductase reaction in the biosynthesis of cholesterol

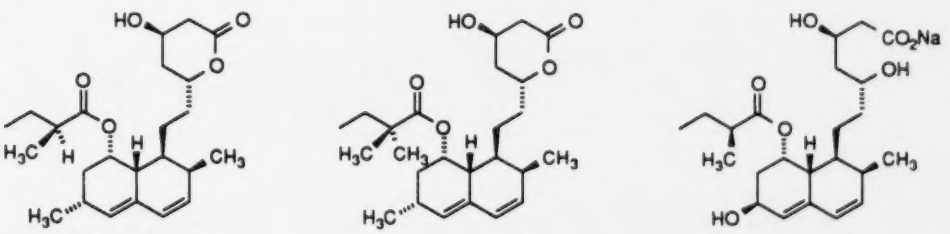


Lovastatin (**5**) is administered as the inactive lactone prodrug which is converted to its dihydroxy open acid form (**5a**) in the liver.[38] This form mimics the structure of the

proposed intermediate in the first reduction step of HMG-CoA (Figure 11). An inhibition constant of 6.4 x 10^{-10} M for the open acid form on HMG-CoA reductase[33] can be compared to the Michaelis constant of 4.0 x 10^{-6} M for the substrate, HMG-CoA.[37] The tight binding of the drug relative to the substrate derives from the simultaneous interaction with the HMG-CoA binding pocket and the adjacent hydrophobic pocket. The interaction in the latter region is not utilized in substrate binding.[39] The decrease in the production of hepatic cholesterol by the inhibition of HMG-CoA reductase causes an increase of LDL receptors.[40] The number and activity of hepatic receptors is an important determinant of LDL clearance from the bloodstream, therefore the increase in LDL receptors leads to a decrease in the LDL level in the blood.[40]

The development of mevastatin (**4**) and lovastatin (**5**) has spawned efforts to identify and synthesize derivatives with improved properties.[41] Two of these drugs currently on the market are simvastatin (**6**) (MK-733, synvinolin, ZOCOR™) and pravastatin (**7**) (CS-514, SQ 31,000, eptastatin) (Figure 12).

Figure 12. Structure of lovastatin (**5**) and related derivatives

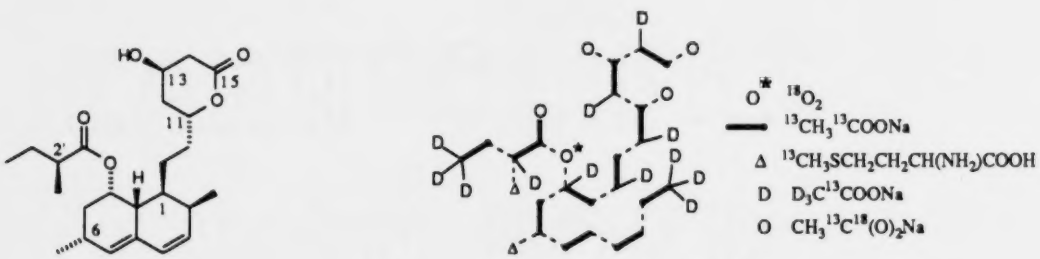


The former is a semisynthetic inhibitor derived from lovastatin (**5**) by modification of the acyl group at C-8 to a 2,2-dimethylbutyrate[42] and is 2.5 times more potent an inhibitor of HMG-CoA reductase than **5**. Pravastatin (**7**), originally found in the urine of dogs treated with mevastatin (**4**),[43] is formed industrially by microbial transformation of **4**.[44]

Although pravastatin is 4 times less active than **5**, it has been found to be more tissue-selective than lovastatin (**5**) or simvastatin (**6**).[45]

Extensive studies of the biosynthesis of lovastatin (**5**) illustrate that the metabolite is formed *via* a polyketide pathway.[46-50] Incorporations of ^{13}C-, ^{2}H-, and ^{18}O-labeled acetates and ^{13}C-methionine into lovastatin by cultures of *Aspergillus terreus* ATCC 20542 show that the main structural unit consists of nine intact acetate units coupled in a head-to-tail fashion with a methionine-derived methyl group at C-6 (Figure 13).[46a] In actinomycetes the methyl and ethyl side chains usually result from the incorporation of propionate and butyrate units;[51] however, the methyl side chains in fungi originate from the incorporation of acetate into the polyketide followed by C-methylation *via* S-adenosyl methionine.

Figure 13. Origins of hydrogen, carbon, and oxygen atoms in lovastatin (**5**)



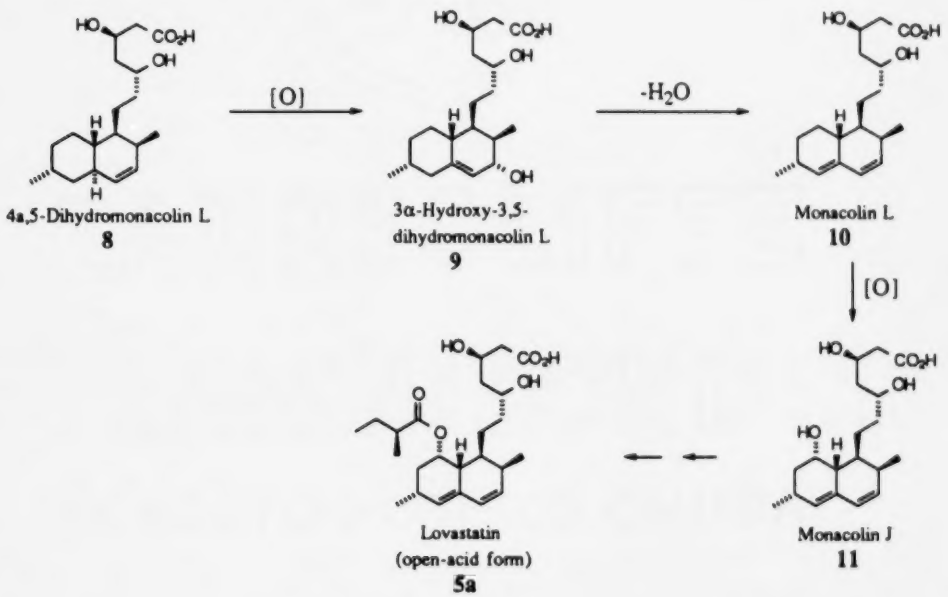
Lovastatin
5

Biosynthetic Distribution

The β-methylbutyryl side chain is similarly constructed from two acetate units, with a methyl group at C-2' donated by methionine. The sources of the carbon-oxygen bonds were reexamined using cultures of *Aspergillus terreus* MF 4845.[50] The oxygens at C-11, C-13, and C-15, initially accounted for by the aerobic oxidation of a deoxygenated precursor, are in fact acetate derived, at least in this organism.[50]

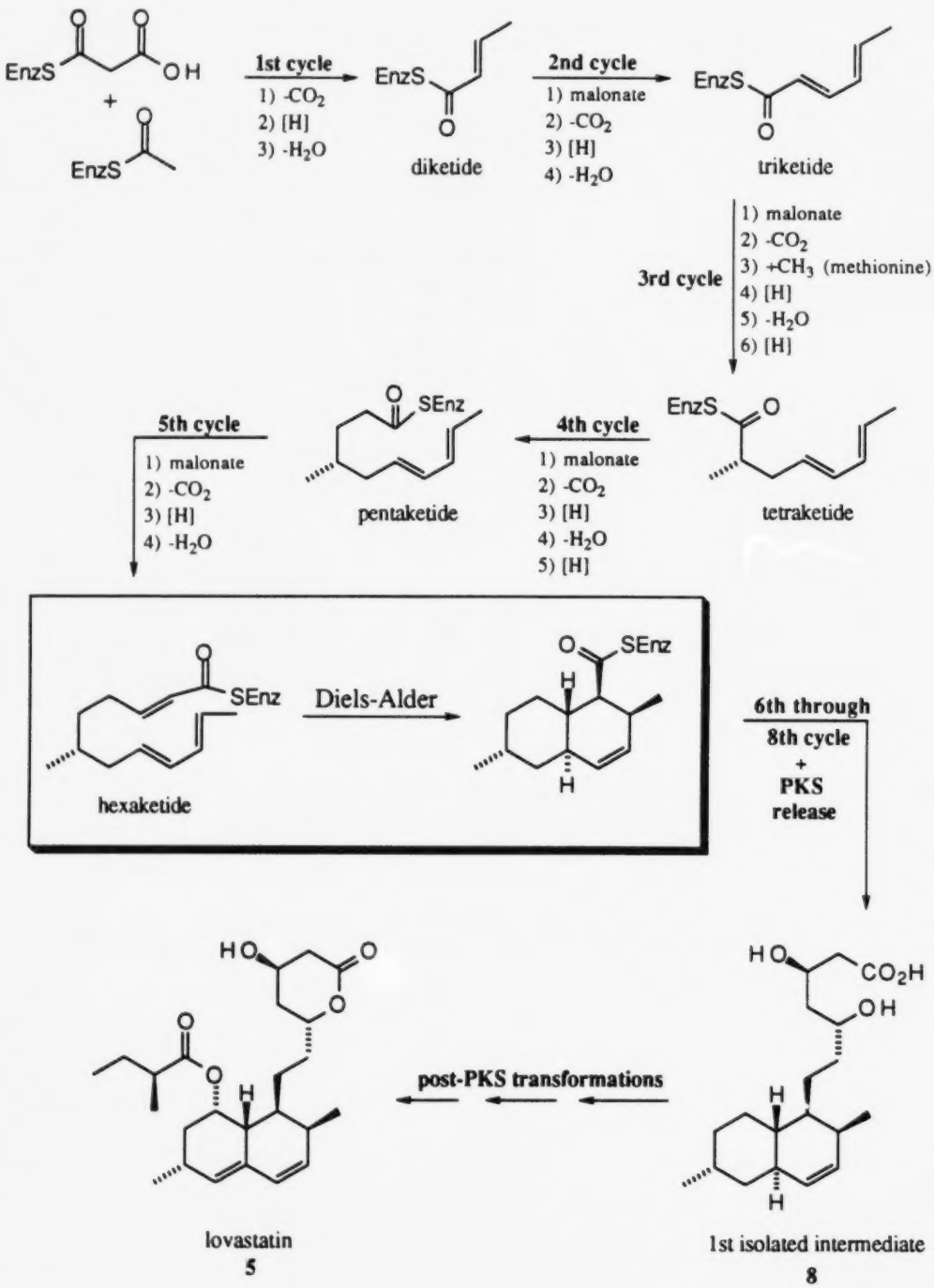
The post-PKS intermediates in the biotransformation of lovastatin from *Monascus ruber* have been examined by Endo and coworkers.[52-55] The earliest isolated intermediate and postulated product of the PKS, 4a,5-dihydromonacolin L (**8**),[52] is converted to 3α-hydroxy-3,5-dihydromonacolin L (**9**) by cell-free extracts of *M. ruber* in the presence of molecular oxygen (Scheme 4).[53] Treiber *et al.* also isolated **9** as its phenacyl ester from a culture broth of *Aspergillus terreus*.[56] The unstable allylic alcohol **9** eliminates water to give monacolin L (**10**),[53] which is hydroxylated to monacolin J (**11**) by molecular oxygen in the cell-free system.[54] The final step involves the esterification of monacolin J (**11**) to the open-acid form of lovastatin (**5a**).[55]

Scheme 4.



The intermediates in the PKS pathway up to the first enzyme-free intermediate **8** remain unknown, but current theories allow us to postulate how **8** is formed. The suggested pathway (Figure 14), following typical polyketide assembly reactions, produces the diketide by condensation of acetate and malonate followed by β-keto reduction and dehydration.

Figure 14. Proposed assembly of lovastatin (**5**) *via* the polyketide pathway



Another malonate extension, reduction and dehydration delivers the triketide, which can be processed through three more PKS cycles to the hexaketide. According to this hypothesis, the diene and dienophile moieties of the hexaketide would undergo an intramolecular Diels-Alder reaction to form the bicyclic core of lovastatin (**5**), thereby producing the stereochemistry found in the first isolated intermediate, 4a,5-dihydromonacolin L (**8**). The unprecedented enzyme-catalyzed Diels-Alder reaction has been suggested in several biosynthetic pathways of natural products.[12b, 57-63] The resultant decalin system could then be chain extended until its release from the PKS at the nonaketide stage.

Recent success with intact incorporations of di- and tetraketide intermediates into their respective polyketide products[8-14] prompted us to investigate the biosynthesis of lovastatin (**5**). In the hypothesis postulated for the biosynthesis of **5** (Figure 14), the most interesting polyketide intermediate leading to the formation of 4a,5-dihydro-monacolin L (**8**) is the hexaketide, since there is a possibility of an intramolecular cyclization. We envisioned that the synthesis of the hexaketide would provide insight into the possibility of a biological Diels-Alder reaction by providing information about its propensity to cyclize and about the stereochemistry of the cyclized products. Isotopic labeling of the hexaketide would also generate a precursor that could be fed to a producing strain of *Aspergillus terreus* to test whether the hexaketide is a biosynthetic intermediate in the formation of the metabolite, thereby providing support for an enzyme-catalyzed Diels-Alder reaction.

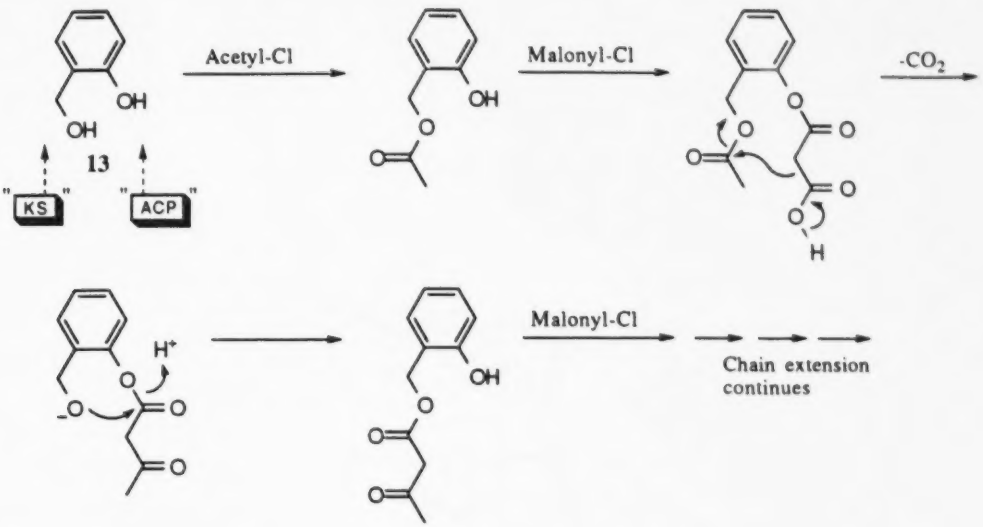
RESULTS AND DISCUSSION

MODEL STUDY OF POLYKETIDE BIOSYNTHESIS

Biomimetic Model Using a 2-Hydroxybenzyl Alcohol Template

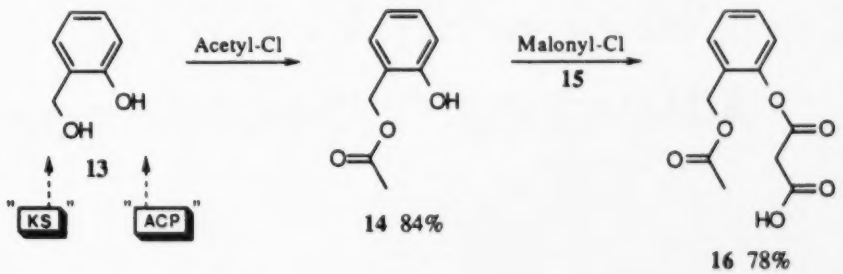
In order to explore mechanistic details of polyketide formation a simple chemical template which could mimic the acylation step would be a valuable tool. An appropriate and synthetically useful mimic should contain the following features: a simple and easily-accessible bifunctional template; two distinct attachment sites, so that one acts as the equivalent of the β-ketoacyl carrier protein synthase and the other as the acyl carrier protein; and an intramolecularly feasible condensation reaction. Earlier work by Scott[24] investigated a model using catechol (**12**) as a template. However, this system contains two equivalent hydroxyl groups and therefore one cannot distinguish between the two sites of acyl attachment. The introduction of a methylene group between one hydroxyl group and the aromatic ring of catechol (**12**) would render the two hydroxyl groups distinguishable. Commercially available 2-hydroxybenzyl alcohol (**13**) contains both an aromatic and a primary hydroxyl group and was the first template we studied (Figure 15). The primary hydroxyl group can be selectively acetylated in the presence of the aromatic hydroxyl group leaving the latter free for coupling with a malonate unit. After the intramolecular acetate-malonate condensation reaction, the resultant acetoacetate ligand could in principle be transferred back to the primary hydroxyl group through an intramolecular acyl transfer, since the phenoxide is a better leaving group than the primary alkoxide. This would leave the ring hydroxyl group available for attachment of another malonate and the chain extension could continue.

Figure 15. Proposed intramolecular condensation using 2-hydroxybenzyl alcohol model



Thus, reaction of 2-hydroxybenzyl alcohol (**13**) with acetyl chloride and *N*,*N*-dimethylaniline gives 2-hydroxylbenzyl acetate (**14**). Condensation of monoacetate **14** with the half acid chloride of malonic acid (**15**)[64] in refluxing THF generates the desired 2-acetyloxymethyl-1-phenyl malonate (**16**) (Scheme 5).

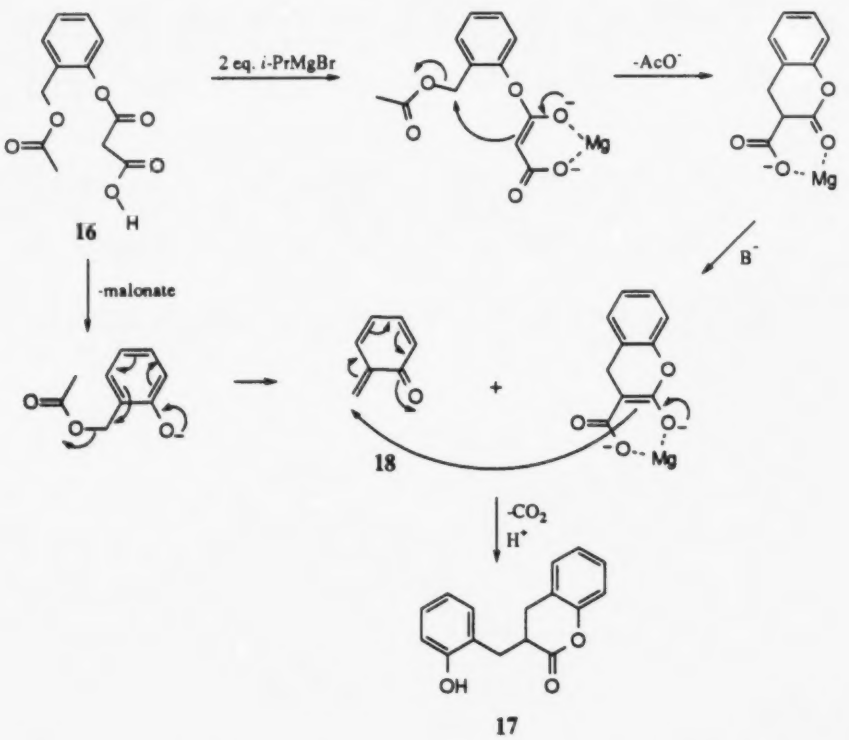
Scheme 5.



Magnesium chelation was postulated to be essential in Scott's catechol model since the intramolecular condensation reaction failed in its absence. Hence the condensation reaction of **16** was initially attempted using $MgBr_2 \cdot Et_2O$,[65] but this material

failed to effect reaction. Compound **16** was then subjected to various amounts of isopropyl magnesium bromide (1.3, 2.0, 3.0 equivalents)[66] in THF at room temperature, but in each case a mixture of four or more products was generated (by TLC). Two of the compounds isolated from the reaction with two equivalents of *i*-PrMgBr are unreacted **16** (32%) and 3-(2-hydroxybenzyl)-dihydrocoumarin (**17**) (25%). COSY, HMQC, and HMBC NMR spectra confirm the structure of **17**, which probably forms *via* the highly reactive enone species **18**, as shown in Figure 16. The possible existence of this enone **18** illustrates that the ring system can allow the facile displacement of the benzylic acetate. This inherent problem with the 2-hydroxybenzyl alcohol template precluded its use in further studies. The apparent success, although limited (30% yield of catechol acetoacetate),[24] with catechol (**12**) as a matrix prompted us to reinvestigate this system before developing a new template.

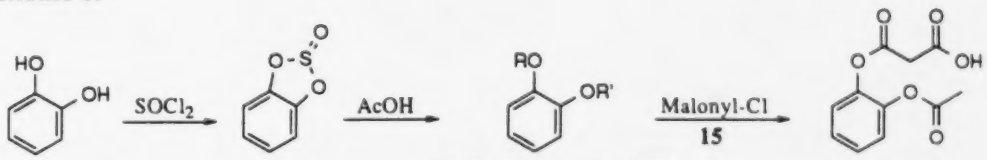
Figure 16. Possible pathway leading to **17**



Reinvestigation of the Catechol Template

In order to test the reaction protocol used for Scott's model, a sample of catechol acetate malonate (**1**) was prepared (Scheme 6). Selective mono-acetylation of catechol (**12**) is difficult, and two methods were tried to generate the catechol monoacetate (**19**). The first procedure employs acetyl chloride and *N*,*N*-dimethylaniline to produce a 1:1:1 mixture of catechol (**12**): catechol monoacetate (**19**): catechol diacetate (**20**), which must be separated. Alternatively, acetolysis of thionyl catechol (**21**)[67] generates a 2:2:1 mixture of the three compounds. Hence acetylation with acetyl chloride is the preferable method. Condensation of the monoacetate **19** with malonate monochloride (**15**) in refluxing ether gives catechol acetate malonate (**1**).

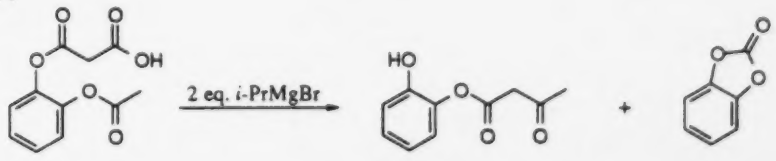
Scheme 6.



12 **21** 74% **19** R = H, R' = Ac 27% **20** R = R' = Ac 14% **12** R = R' = H 27% **1** 63%

The published conditions for the intramolecular condensation reaction with the catechol acetate malonate (**1**) are treatment with 2 molar equivalents of fresh isopropyl magnesium bromide in THF at room temperature for 3 h.[24] This gives catechol monoacetoacetate (**2**) and catechol carbonate (**3**) after acidic work-up (Scheme 7).

Scheme 7.

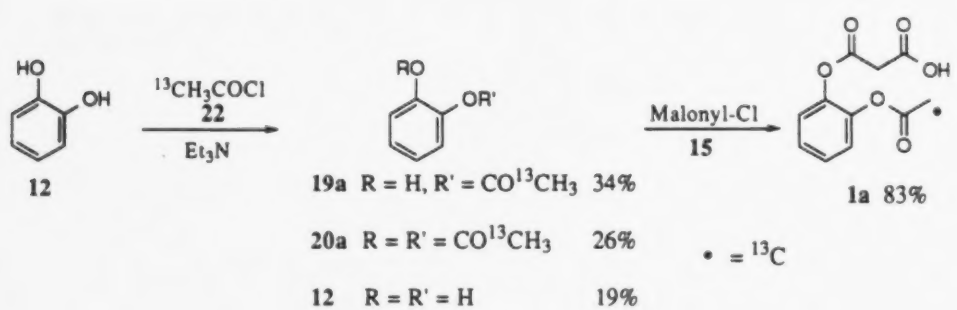


1 **2** 10% **3** 30%

The catechol monoacetoacetate (**2**) could be identified by comparison with an authentic sample synthesized from catechol (**12**) and diketene in refluxing toluene. The low yield in the reaction can be attributed to the facile hydrolysis of the products during the isolation procedure. This sequence illustrates that the same conditions that lead to decomposition of the 2-hydroxybenzyl alcohol model (**16**) generate the acetoacetate product from this catechol-based system.

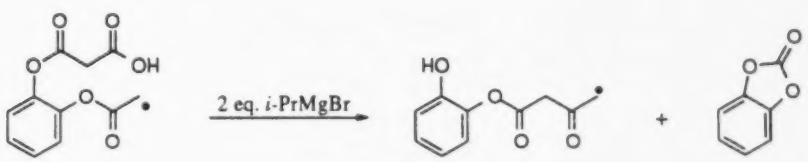
Before developing another template for the biomimetic system, the acetyl transfer reaction in the catechol acetate malonate (**1**) system was studied further through the use of a ^{13}C-labeling experiment. Two control experiments suggest that the condensation reaction is intramolecular: resorcinol acetate malonate fails to give resorcinol monoacetoacetate under conditions identical to those used in the original experiment; and magnesium monoethyl malonate fails to condense with catechol monoacetate using the same conditions.[24] To test whether any catechol monoacetoacetate results from enolate formation at one acetate and intermolecular condensation with another acetate, the catechol [2-^{13}C]acetate malonate (**1a**) was prepared (Scheme 8). Reaction of labeled sodium [2-^{13}C]acetate (isotopic purity 99% ^{13}C) with PCl_5 generates the corresponding acetyl chloride (**22**),[68] required for the synthesis of the labeled system.

Scheme 8.



Treatment of **1a** with isopropyl magnesium bromide causes acetyl transfer to occur with all the ^{13}C-label residing on the methyl group of the acetoacetate moiety in **2b** (Scheme 9). This indicates that the condensation proceeds solely by malonate enolate formation and supports the original pathway from catechol acetate malonate (**1**) proposed by Scott and coworkers.[24]

Scheme 9.

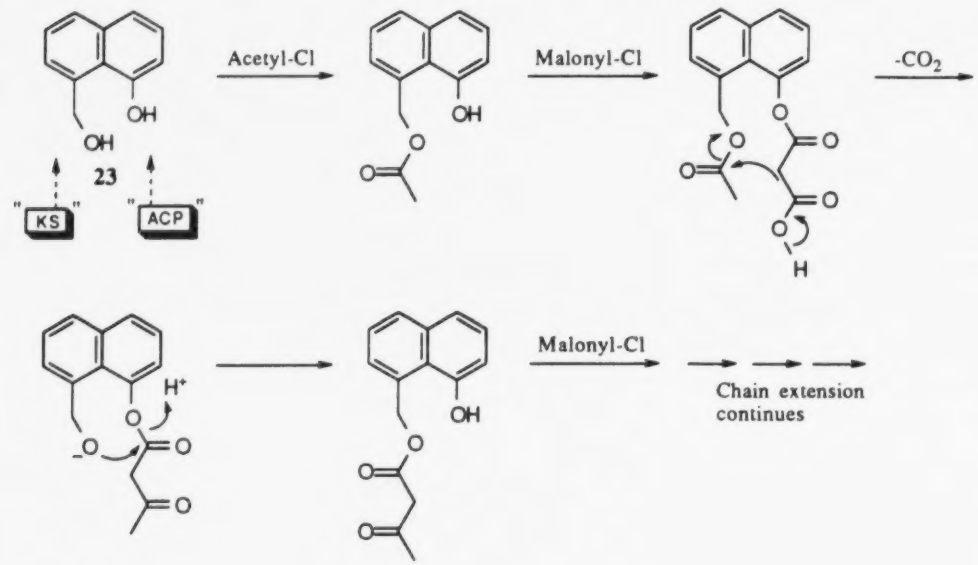


1a • = ^{13}C **2b** 21% **3** 30%

Biomimetic Model Using a 8-Hydroxy-1-naphthalenemethanol Template

Evidence for the intramolecular condensation reaction in the catechol model **1** suggests possible extension of this system for a second template. A key requirement is to have two different sites of attachment to more closely mimic the natural system. Hence insertion of a methylene group between the hydroxyl group and aromatic ring is still attractive provided that acetate expulsion seen with the 2-hydroxybenzyl alcohol derivative **16** can be supressed. The aromatic hydroxyl and the hydroxymethyl groups should ideally be situated on a rigid ring system, yet be close enough for the reaction to take place. A potential template that satisifies these requirements is 8-hydroxy-1-naphthalenemethanol (**23**) (Figure 17). A sequence of steps for the internal condensation reaction similar to those seen in Figure 15 can also be envisaged with **23** (Figure 17).

Figure 17. Proposed intramolecular condensation using 8-hydroxy-1-naphthalenemethanol model

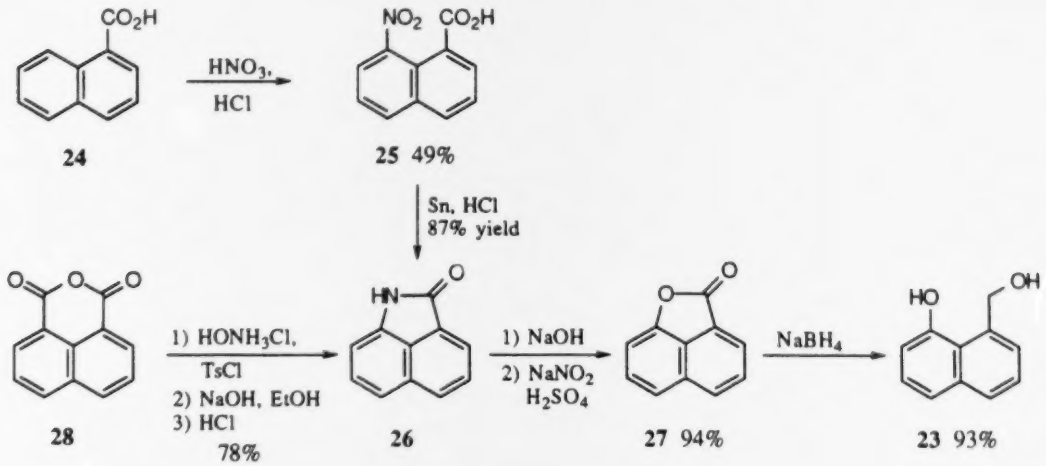


After a selective functionalization with acetate and malonate on the primary and ring hydroxyl groups, respectively, the system could undergo an intramolecular condensation in the presence of a base to deliver the acetoacetate ligand. The acetoacetate thus formed could also be expected to be transferred back to the primary hydroxyl group. The chain could in principle then be extended by further attachments of malonate and condensation reactions.

The synthesis of the 8-hydroxy-1-naphthalenemethanol (**23**) template was achieved by two different pathways. In the first, nitration of 1-naphthoic acid (**24**) with concentrated HNO_3 and HCl generates 8-nitro-1-naphthoic acid (**25**), 5-nitro-1-naphthoic acid, and 6,8-dinitro-1-naphthoic acid which can be separated (Scheme 10).[69] Reduction of **25** and subsequent lactam formation in the presence of tin and concentrated HCl[70] gives the tricyclic amide **26**. Saponification, diazotization and hydrolysis of the lactam **26** generates the corresponding lactone **27**.[71-72] The lactone **27** reacts rapidly

with sodium borohydride to give 8-hydroxy-1-naphthalenemethanol (**23**),[73] although γ-lactones are not usually reduced by this reagent.[74]

Scheme 10.

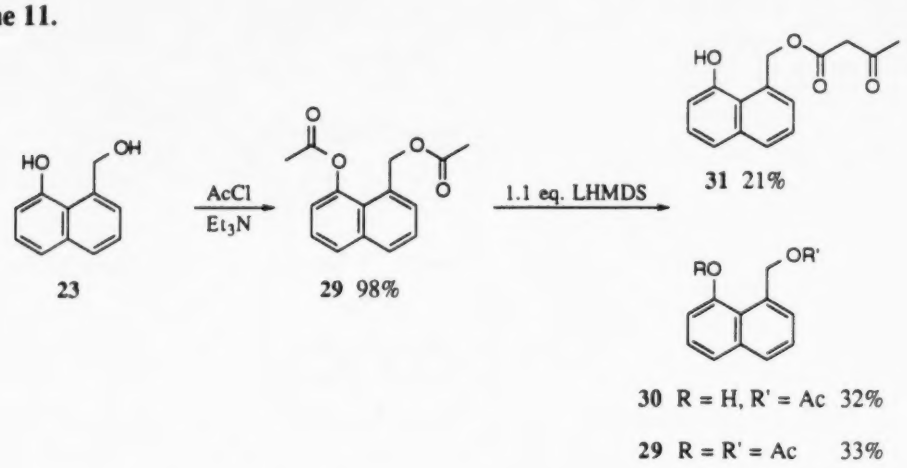


The ring strain of the lactone may explain its heightened reactivity; 8-hydroxy-1-naphthoic acid fails to lactonize under acidic conditions, even though it is a γ-hydroxy-acid.[73] A more efficient synthesis of **23** begins with the conversion of naphthalic anhydride **28** to the lactam **26** by condensation with hydroxylamine, to give a hydroxyimide.[72] Esterification of the imide with 4-toluenesulphonyl chloride followed by a Lossen-type rearrangement in ethanolic sodium hydroxide and subsequent decarboxylation allows lactam formation in acidic conditions. The advantage of this route is that the lactam **26** can be prepared without intermediate purification in 78% yield compared with two steps and a combined yield of 42% for the former method.

With the 8-hydroxy-1-naphthalenemethanol template **23** available, a series of experiments was attempted to study the viability of this material as a suitable mimic of the natural system. To test whether simple acyl transfer could occur, the diacetylated material **29** was exposed to 1.1 equivalents of lithium hexamethyldisilazane (LHMDS) in THF. These conditions generate three compounds: monoacetylated **30**, diacetylated **29**,

and the desired monoacetoacetate product **31** (Scheme 11). Comparison with an authentic sample synthesized from the diol and diketene in refluxing THF confirms the structure of monoactoacetate **31**. This result is promising since the acetoacetate ligand is attached to the desired benzylic hydroxyl group.

Scheme 11.



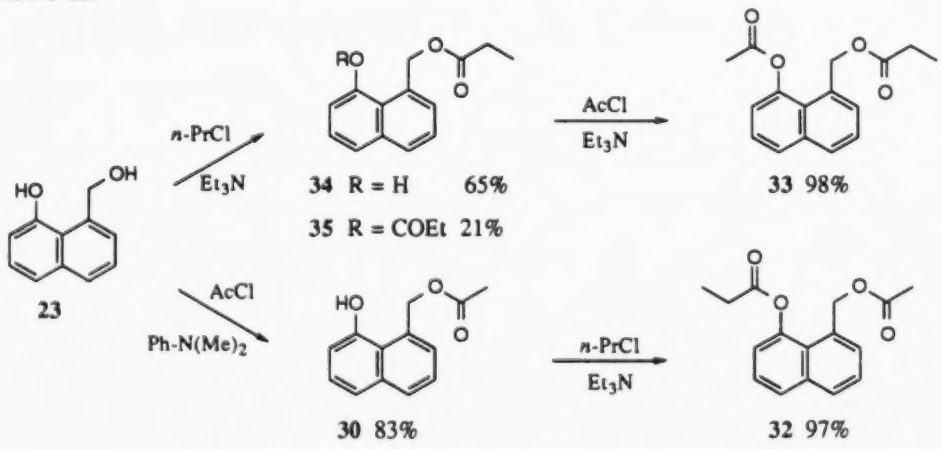
23 **29** 98% **31** 21%

30 R = H, R' = Ac 32%

29 R = R' = Ac 33%

A key question is which enolate is preferentially formed; this can be addressed by examining the two regioisomers of the propionyl and acetyl esters of 8-hydroxymethyl-1-naphthalenemethanol (**23**). Treatment of the diol **23** with acetyl chloride and *N,N*-dimethylaniline selectively affords monoacetylated material **30** (Scheme 12).

Scheme 12.



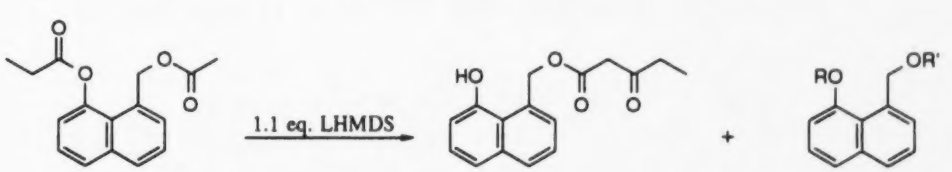
23 **34** R = H 65% **35** R = COEt 21% **33** 98%

30 83% **32** 97%

Reaction of the naphthol **30** with *n*-propionyl chloride then generates one regioisomer **32**. The other regioisomer **33** is available similarly by preparation of the monopropionyl derivative **34** and subsequent acetylation (Scheme 12).

Treatment of regioisomer **32** with LHMDS generates a mixture of four products (Scheme 13). The presence of **36** as the only isolated condensation product suggests reasonable regioselectivity, with the base preferring to deprotonate the less hindered acetyl group with the lower pK_a. However formation of **34** indicates that acyl transfer is also occurring. Thus, the acyl groups are able to transfer from the phenoxide to the alkoxide and back under these reaction conditions. Since the intermolecular transfer (or scrambling) of the acyl groups occurs, the formation of the condensation product **36** may not be an intramolecular process, but rather an intermolecular condensation. The reaction with the other regioisomer **33** was not performed in order to address the more immediate question of whether intermolecular condensations were occurring.

Scheme 13.



32

36 30%

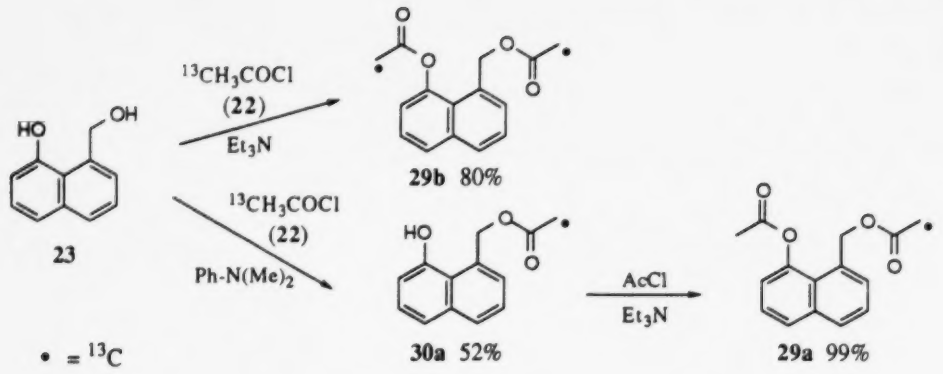
32 R = COEt, R' = Ac 34%

30 R = H, R' = Ac 12%

34 R = H, R' = COEt 4%

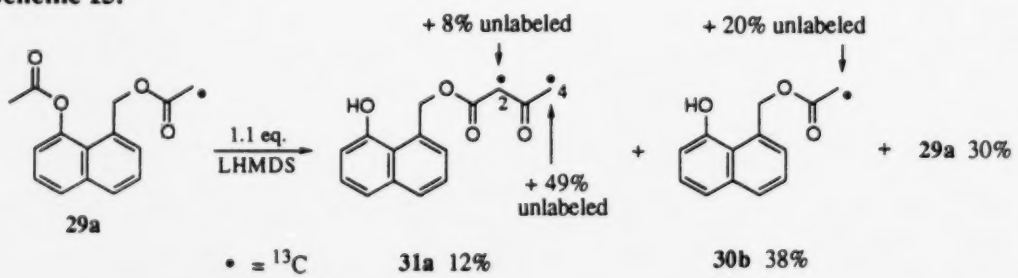
To investigate the intermolecular versus intramolecular process, the diacetylated material was synthesized in singly and doubly ^{13}C-labeled forms (**29a** and **29b,** respectively) using [2-^{13}C]acetyl chloride **22** (isotopic purity 99% ^{13}C) (Scheme 14).

Scheme 14.



The singly-labeled material **29a** bears the ^{13}C-label on the methyl group of the acetate, so if the base deprotonates this acetate and the intramolecular condensation reaction occurs, then the ^{13}C-label in the resultant acetoacetate ligand would reside on the methylene group. If the deprotonation occurs on the acetate directly attached to the ring and intramolecular condensation takes place, the ^{13}C-label would then be located on the methyl group in the acetoacetate ligand. A 1:1 combination of these two processes would lead to a maximum 50% ^{13}C-label in each position and any permutation in between should give a total of 100% ^{13}C-label for both positions. In the presence of LHMDS, singly-labeled material **29a** produces monoacetate **30b**, unreacted **29a**, and monoacetoacetate **31a** (Scheme 15). Integration of the C-4 methyl and C-2 methylene ^1H NMR signals of **31a** allows calculation of the percentage of ^{13}C-labels at each position by comparison of the labeled and unlabeled signals.

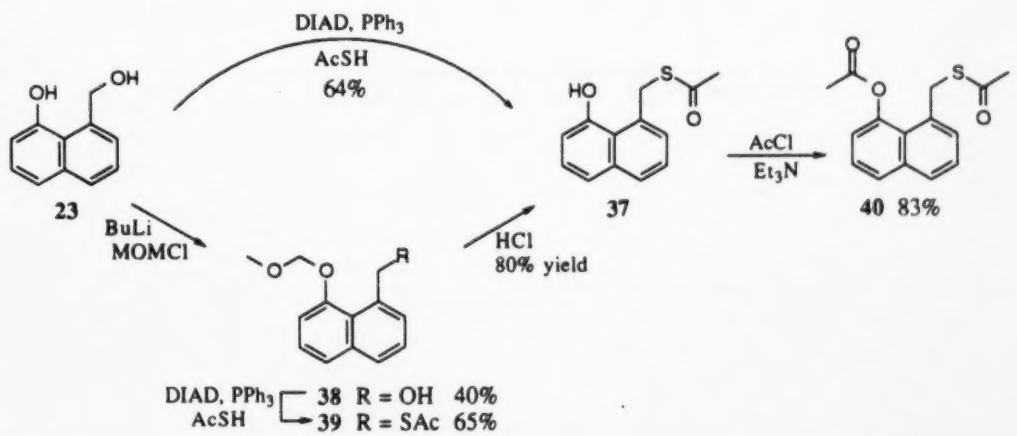
Scheme 15.



Out of the 12% isolated monoacetoacetate **31a**, 92% of the material possesses label in the C-2 methylene position which leaves only 8% of the material to be labeled in the C-4 methyl position if the condensation reaction occurs intramolecularly. However, 51% of the compound **31a** is actually labeled in the C-4 methyl position, far exceeding the expected limit. This suggests that intermolecular condensations are occurring between the labeled acetates on different molecules. The isolated monoacetate **30b** is 20% unlabeled in the C-2 methyl position suggesting that acyl transfer or scrambling is also a problem.

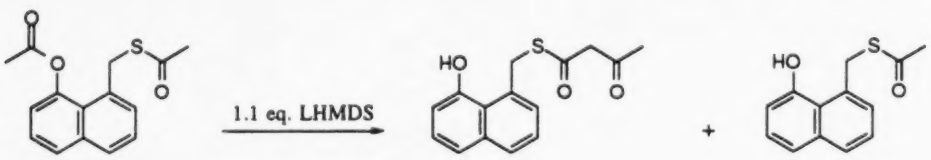
Another system we investigated replaces the primary hydroxyl group with a thiol to determine the effect of a thioester on the template. The thioester **37** can be synthesized by two routes (Scheme 16). The first approach involves protection of the phenoxy group as the methoxymethyl ether **38**, followed by treatment with thioacetic acid using Mitsunobu conditions[75] to give the protected thioester **39**. Deprotection under acidic conditions generates the naphthol **37**. The protection/deprotection step can be avoided using Mitsunobu conditions directly on the diol **23**. Treatment with acetyl chloride then affords the diacetylated material **40**.

Scheme 16.



Base treatment of this thioester **40** as above gives the monoacetate **37** and the monoacetoacetate **41** compounds (Scheme 17).

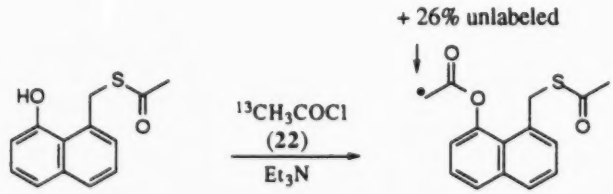
Scheme 17.



40 **41** 31% + **37** 40%

To determine whether an intramolecular or intermolecular condensation occurs, the labeled thioester was synthesized. Such labeling also allows determination of which enolate (ester or thioester) is formed in the intramolecular case. Treatment of thioester **37** with [2-^{13}C]acetyl chloride (**22**) and triethylamine gives the diacetylated material **40a** (Scheme 18). However, the ^{1}H NMR spectrum indicates that the methyl group of the newly formed ester **40a** is 26% unlabeled. Since the [2-^{13}C]acetyl chloride (**22**) possesses 99% isotopic purity, this result indicates scrambling of the acetyl groups between the two sites of acyl attachment on the same or different molecules. It seems that the thioester has a higher susceptibility for acyl transfer than the *O*-ester, since no scrambling is observed in the formation of singly ^{13}C-labeled diacetate **29a**; therefore base treatment of this diacetylated material **40a** was not attempted.

Scheme 18.

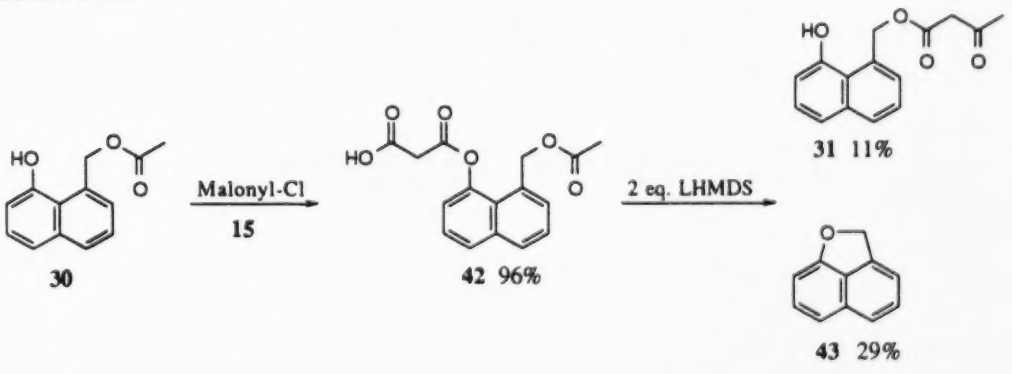


37 **40a** 63%

• = ^{13}C

The chain elongation step in polyketide formation involves an intramolecular reaction between the enzyme-bound acetate and malonate with simultaneous loss of carbon dioxide. Thus the condensation reaction with a malonate derivative of the naphthalene template could potentially function more effectively than the diacetyl system **29** described above. Condensation of monoacetate **30** and malonate monochloride (**15**) in refluxing THF gives the malonate acetate system **42** (Scheme 19). Treatment of this compound with a variety of bases under various conditions (LDA, *n*-BuLi, NaH, imidazole, and *i*-PrMgBr) failed to produce the desired product **31**. Only in the presence of two equivalents of LHMDS could the acetoacetate **31** be detected (Scheme 19). Heating the mixture in the last stages of the reaction to generate more acetoacetate product **31** fails and leads to the formation of the 2H-naphtho-[1,8-bc]-furan (**43**),[76] probably due to attack at the benzylic carbon by the phenoxy group with subsequent loss of the acyl unit. The formation of acetoacetate **31** indicates occurrence of either an intra- or intermolecular reaction. Labeling experiments allow this to be investigated.

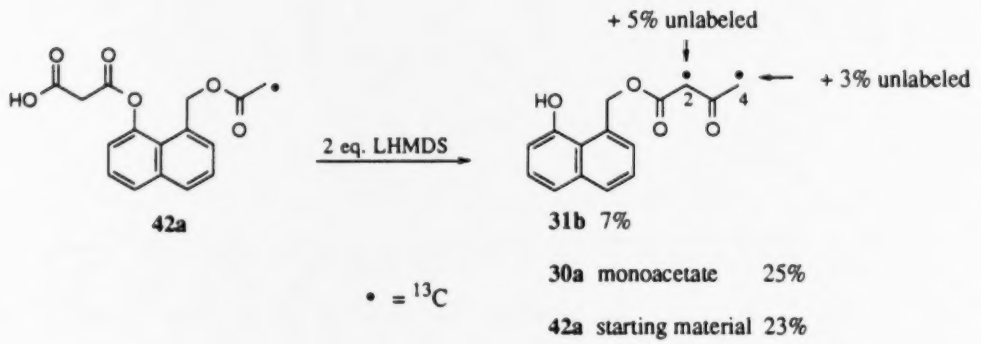
Scheme 19.



29	diacetate	2%
30	monoacetate	9%
42	starting material	22%

The malonate derivative **42a**, produced in 93% yield from labeled monoacetate **30a**, bears ^{13}C-label at the methyl position of the acetate group (Scheme 20). If the reaction is an intramolecular condensation *via* enolate formation of the malonate, then the resultant acetoacetate product should have all the label residing on the C-4 methyl group. Exposure of labeled **42a** to the required basic conditions gives the isolated acetoacetate **31b** which is 97% ^{13}C-labeled at the C-4 methyl position as well as 95% ^{13}C-labeled at the C-2 methylene position. Hence the intermolecular condensation seems to be the major pathway for the reaction (Scheme 20).

Scheme 20.



The easily accessible 8-hydroxy-1-naphthalenemethanol template **23** satisfies the requirement of having two distinct sites for acyl attachment to sequentially add an acetate and a malonate. The above reactions illustrate that in solution the naphthalene system is capable of acyl transfer *via* an intermolecular process. However, the intramolecular condensation could possibly be favored if the intermolecular process were hindered, which might be achieved by affixing the aromatic model to an insoluble solid support. Solid-supported synthesis has greatly facilitated the formation of polypeptides[77] (e.g. the Merrifield synthesis) and polynucleotides[78] and could potentially eliminate this intermolecular involvement allowing for only intramolecular acylation and switch-over. The use of this type of system remains to be explored.

SYNTHETIC AND BIOSYNTHETIC STUDIES ON LOVASTATIN

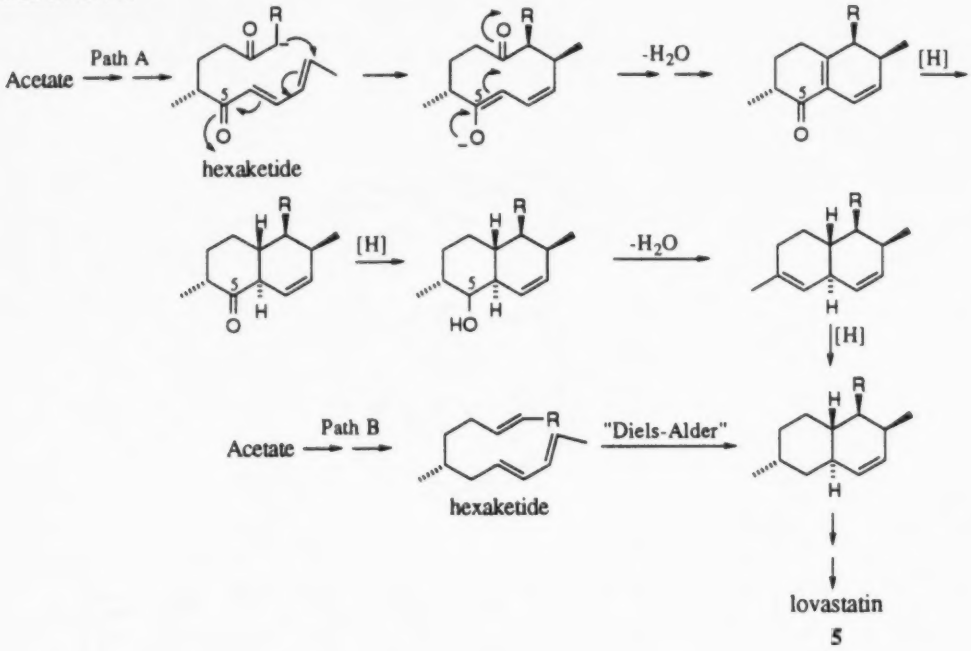
Introduction: Bicyclic Ring System of Lovastatin and the Hexaketide Precursor

Polyketides, as described in the introduction, are believed to be produced by a process analogous to the formation of fatty acids. However, in their biosynthesis the growing polyketides can bypass certain reductive steps, in particular cycles leading to a highly functionalized chain containing keto, hydroxy, olefinic, or methylene moieties. The finding that suitably transformed chain elongation intermediates, administered as their *N*-acetylcysteamine (NAC) thioesters, can be incorporated into various polyketide systems, confirms the stepwise assembly of these metabolites and provides a probe to enable study of their biosynthetic pathways.[8-13] A goal of the present project was to apply similar stategy to the lovastatin system.

Current knowledge of the biosynthetic pathway to lovastatin (**5**) include the origins of the carbon, hydrogen and oxygen atoms and the post-polyketide synthase transformations (see Figure 13 and Scheme 4),[46,52-55] but the preceding intermediates from acetate remain unknown. A primary focus of our interest is the mechanism of formation of the bicyclic skeleton of lovastatin (**5**). This can be rationalized by the two approaches, as shown in Scheme 21, although other possibilities may exist. In path A the polyketide chain is extended to the hexaketide stage while maintaining the keto-oxidation state at C-5. The cyclization can proceed by intramolecular Michael and aldol condensations which are well precedented in the biosynthesis of aromatic compounds.[79] Once the bicyclic structure is formed the ketone function is removed by reduction, dehydration, and a final reduction. In the second pathway, B, the hexaketide is delivered from typical polyketide reactions with the correct oxidation state already attained at C-5. The decalin system resulting from a projected enzyme-catalyzed Diels-Alder cyclization possesses the stereochemistry of the first isolated metabolite,

4a,5-dihydromonacolin L (**8**). This mechanism is attractive since no further elaboration of the bicyclic core is required other than extention of the polyketide chain to include the dihydroxy acid portion of lovastatin (**5**).

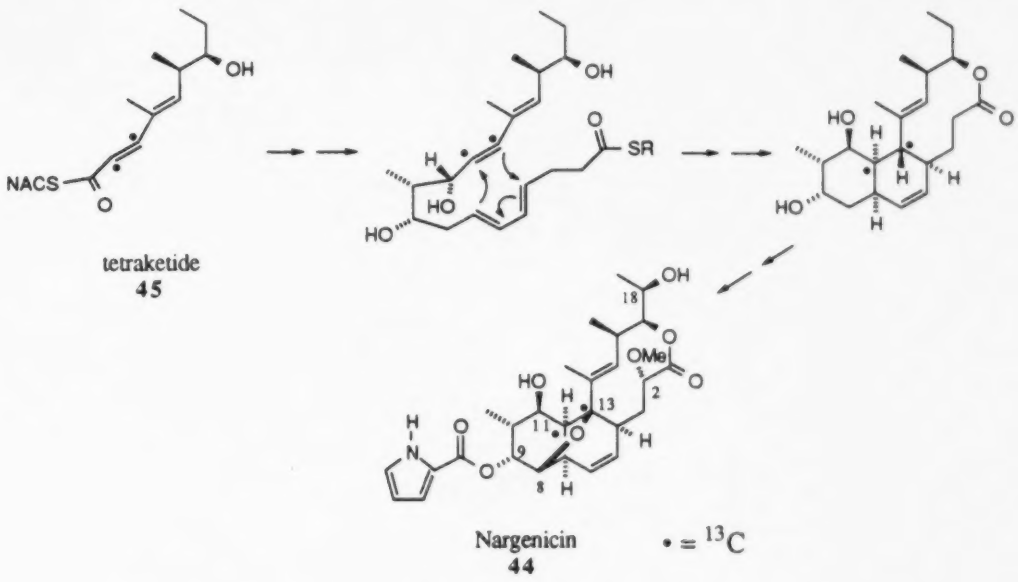
Scheme 21.



Although there are no confirmed examples of enzyme-catalyzed Diels-Alder reactions, this process has been postulated in several biosynthetic pathways and much circumstantial evidence is available.[12b,57-63] The polyketide origin of nargenicin (**44**) from cultures of *Nocardia argentinensis* has been confirmed through the use of labeled acetate and propionate, and the oxygen atoms at carbons 2, 8, 13, and 18 are derived from aerobic oxidation (Figure 18).[80,81] The absence of a propionate-derived oxygen at C-13 disfavors cyclization of the polyketide *via* aldol-type condensation, and the acetate and propionate oxygens at C-11 and C-9 eliminate the possibility of epoxy-olefin and epoxy-alcohol cyclization mechanisms. The intact incorporation of the tetraketide **45** lends support to the postulated intramolecular cyclization of an *E*,*E*-diene with an *E*-dienophile

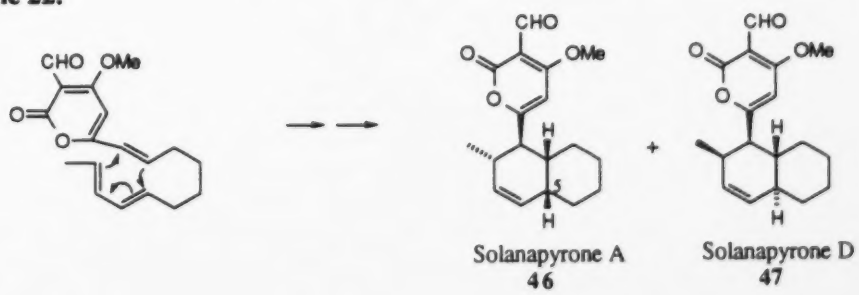
to generate a *cis*-fused decalin ring system with subsequent transformation to nargenicin (**44**).[12b]

Figure 18. Intact incorporation of tetraketide **45** into nargenicin (**44**)



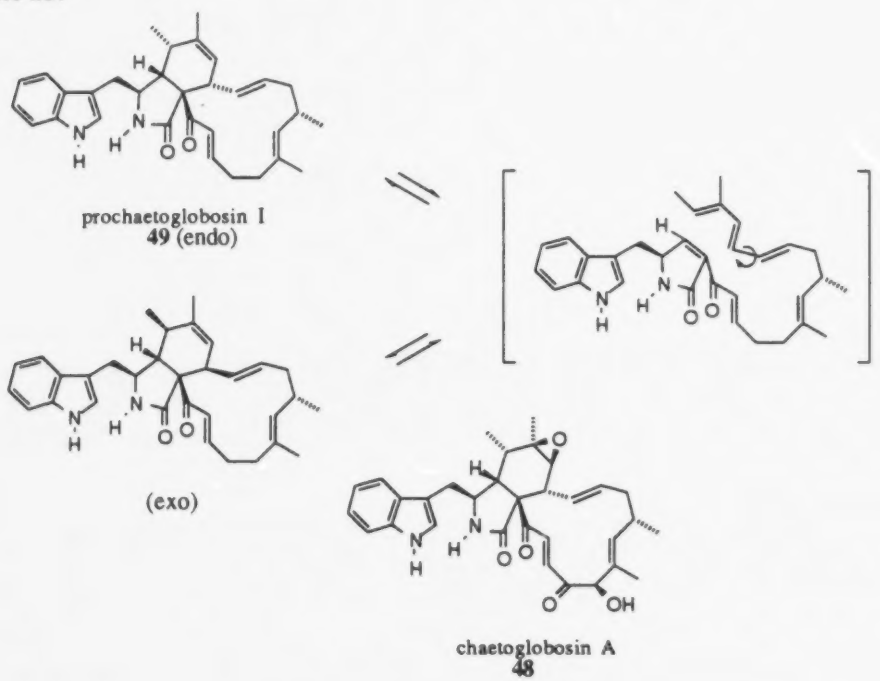
In the biosynthesis of solanapyrone A (**46**) from *Alternaria solani*, an enzyme-catalyzed Diels-Alder reaction is an attractive proposition, since this can account for the stereochemistry and double bond location in the bicyclic ring (Scheme 22). Deuterium retention at C-5 during incorporation of labeled acetate[61] and the co-occurrence of the diastereomer, solanapyrone D (**47**), which could result from *endo* cycloaddition, lend support to the occurrence of a biological Diels-Alder cyclization.[62]

Scheme 22.



A presumed precursor in the biosynthesis of chaetoglobosin A (**48**) from cultures of *Chaetomium subaffine* has been identified during the studies with P-450 oxidation inhibitors, conditions which allow the accumulation of deoxygenated intermediates in sufficient quantities to be isolated.[58] When prochaetoglobosin I (**49**) is subjected to thermolysis it undergoes a retro-Diels-Alder reaction. This demonstrates chemically (in a reverse sense) the putative cycloaddition in the biosynthesis of chaetoglobosin A (**48**) (Scheme 23).

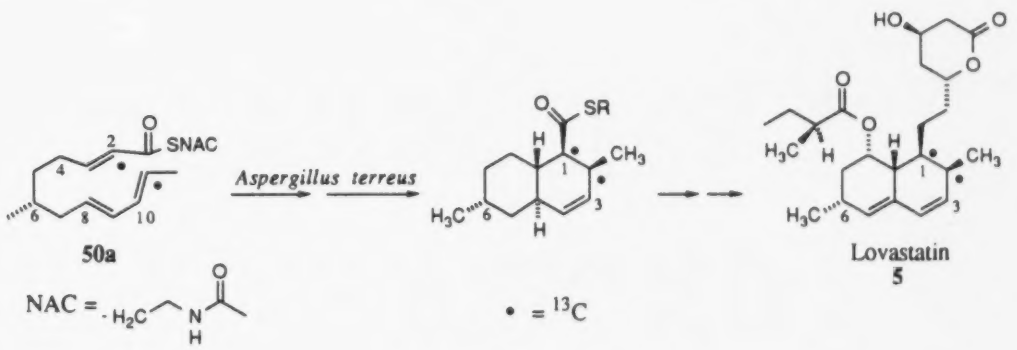
Scheme 23.



In order to investigate the possibility of an enzyme-catalyzed Diels-Alder reaction occurring during the biosynthesis of lovastatin (**5**) and bolster the processive hypothesis of polyketide biosynthesis, the hexaketide **50a** was chosen as a suitable target for feeding experiments. Double-labeling with ^{13}C would be required to detect any oxidative degradation of the precursor prior to its incorporation in the metabolite. It would be extremely unlikely that any singly-labeled materials generated from the oxidative

processes be incorporated with the same label distribution as the intact doubly-labeled precursor. The material **50a** as its NAC thioester would be fed into fermentations of *Aspergillus terreus* to allow its entry into the polyketide synthase (Scheme 24). Once within the synthase the putative Diels-Alder enzyme could cyclize the triene to the decalin system with the same stereochemistry as seen in lovastatin (**5**). The bicyclic hexaketide could then be processed to **5** *via* further chain extensions and post-PKS transformations. Intact incorporation of the labeled precursor could be verified by examination of the ^{13}C NMR spectrum of the isolated lovastatin. The two ^{13}C labels, originally at C-2 and C-11 in the precursor, would become adjacent at C-1 and C-2 in lovastatin, giving rise to two doublets with equivalent coupling constants.

Scheme 24.

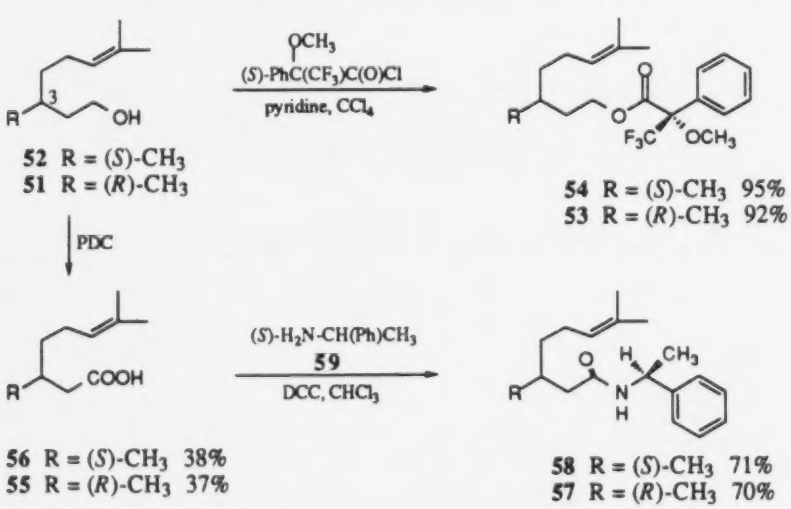


Synthesis of the Hexaketide Precursor

The direct synthesis of the proposed acyclic hexaketide to lovastatin (**5**) would also enable a study of its reactivity. For example, the ease of cyclization *via* Diels-Alder reaction, the nature of the products which are formed, and the stereochemical relationship of the cycloadducts to lovastatin (**5**) are of interest.

The synthesis of the hexaketide should manipulate functionality such that the ^{13}C-labels can be attached at a late stage in the synthetic pathway. (*R*)-Citronellol (**51**), which contains a methyl group at C-3 with the same *R*-configuration as the C-6 methyl substituent in lovastatin (**5**), is a commercially available starting material which is functionalized at both ends (Scheme 25). Since citronellol occurs naturally in both enantiomeric forms, the enantiomeric excess of the commercial (*R*)-citronellol (**51**) must be determined to estimate the purity of the resultant biosynthetic precursor. Two derivatizations were performed on citronellol to calculate its purity. In the first attempt, (*R*)- and (*S*)-citronellol (**51**) and (**52**) were converted to their (*R*)-Mosher esters[82] (**53** and **54**, respectively) (Scheme 25). Comparison of their ^{1}H, ^{13}C, and ^{19}F NMR spectra showed no significant differences in any chemical shift, and the diastereomers could not be separated by reverse phase HPLC. The citronellols **51** and **52** were then converted to their *N*-(1*S*)-phenylethyl amides by oxidation to their corresponding acids,[83] **55** and **56**, followed by amidation to the respective amides,[84] **57** and **58**.

Scheme 25.



52 R = (*S*)-CH_3
51 R = (*R*)-CH_3

54 R = (*S*)-CH_3 95%
53 R = (*R*)-CH_3 92%

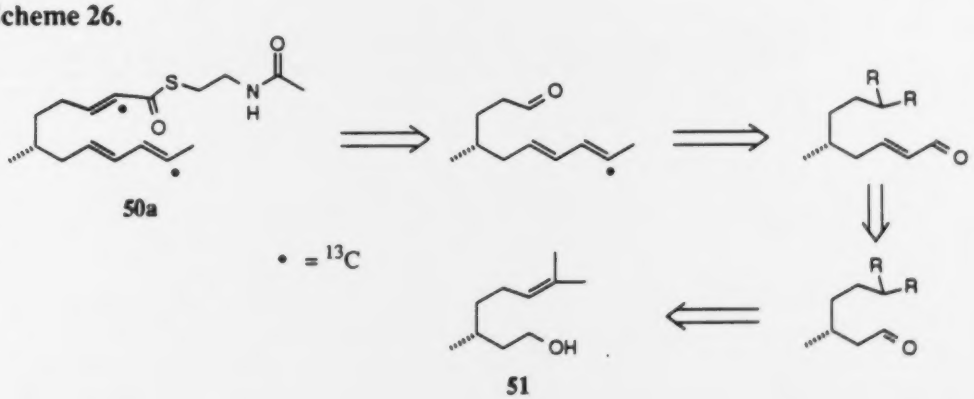
56 R = (*S*)-CH_3 38%
55 R = (*R*)-CH_3 37%

58 R = (*S*)-CH_3 71%
57 R = (*R*)-CH_3 70%

The optical purities of the diastereomers **57** and **58** were then investigated using the optically active NMR chiral shift reagent, tris[3-(heptafluoropropyl-hydroxymethylidene-(+)-camphorato], europium (III) derivative [Eu(hfc)$_3$],[85] but loss of resolution and inadequate separation in the ^{1}H NMR spectra hampered the determination of the diastereomeric ratio by integration. Separation was eventually accomplished by gas chromatography-mass spectrometry (GC-MS). A 5/95 ratio of the two diastereomers was injected and the peaks corresponding to each were integrated *via* total ion current and found to be within ±1% of the original mixture. Other ratios were injected with similar results. There was no detectable second diastereoisomer when pure *N*-(1*S*)-phenylethyl (*R*)-citonellamide (**57**) was tested and since the reagent amine **59** was labeled ≥ 98% pure, the enantiomeric purity of the (*R*)-citronellol (**51**) is also ≥ 98%.

The proposed synthesis of the doubly-labeled *N*-acetylcysteamine (NAC) thioester of the hexaketide **50a** involves functionalizing (*R*)-citronellol (**51**) in a two directional approach, thus minimizing the number of reactions steps required after the incorporation of costly labeled material. The retrosynthetic analysis shown in Scheme 26 illustrates a successive formation of aldehydes which could be transformed to the desired olefins by Wittig chemistry. The construction of the diene, by chain extension from the primary alcohol, is the first target of the synthesis.

Scheme 26.



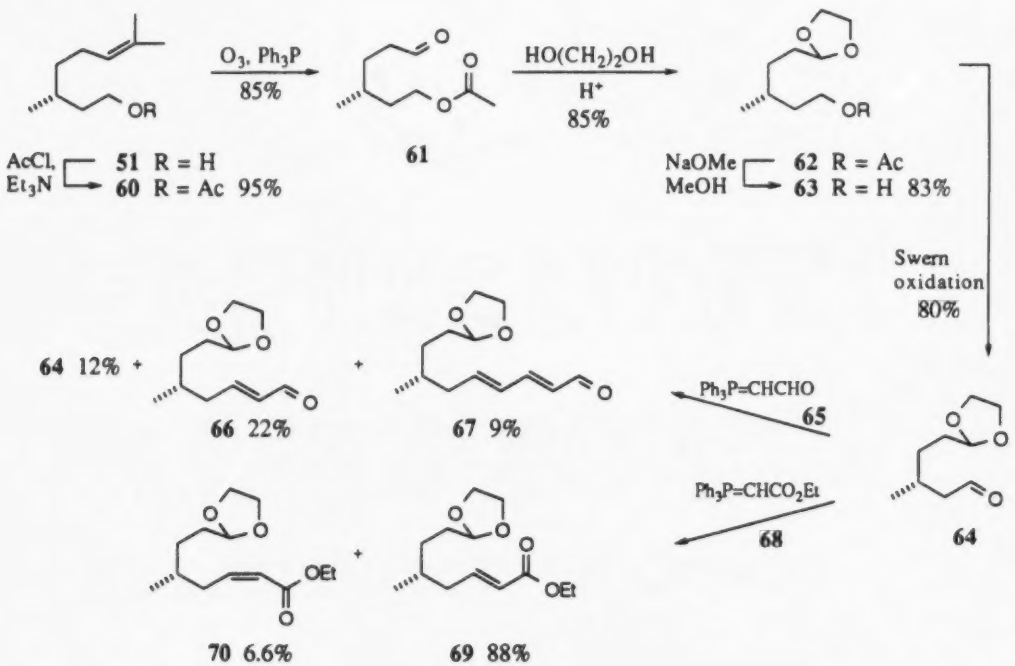
50a

• = ^{13}C

51

Initially, the double bond in citronellol (**51**) must be converted into a protected aldehyde, which would later lead to the desired olefin formation at this site. Ozonolysis at a later stage would be complicated by the inclusion of two further double bonds. Protection of the alcohol **51** as an acetate **60**,[86] followed by sequential treatment[87] with ozone and triphenylphosphine delivers the aldehyde **61**. A second protection[88] with 1,2-ethylene glycol yields the acetal **62** (Scheme 27). Hydrolysis of the acetate **62** and oxidation[89] of the resultant alcohol **63** generates the aldehyde **64**, the substrate for the first double bond attachment.

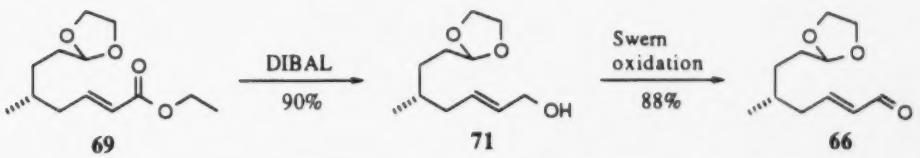
Scheme 27.



Two approaches to generate the first olefin of the diene system were examined (Scheme 27). The first route uses the Wittig reagent (**65**), triphenyl-phosphoranylidene acetaldehyde, since the product from this reaction would be an α,β-unsaturated aldehyde **66**, which would enable the other double bond of the diene to

be attached *via* a second Wittig reaction. This reaction,[90] however, generates a mixture of unreacted aldehyde **64**, desired aldehyde **66**, and over-reacted α,β-γ,δ-dienal **67**, which is difficult to separate. The second, more efficient, method involves reaction of the aldehyde **64** with Wittig reagent **68**[91] to produce a mixture of *E*-and *Z*-isomers (93:7) (**69** and **70**, respectively) in 95% total yield. Separation of the major α,β-unsaturated ester **69** from the minor *Z*-isomer **70** and reduction[92] with DIBAL to the allylic alcohol **71**, followed by Swern oxidization[89] gives the aldehyde **66** (Scheme 28). At this point the second *E*-double bond can be introduced using the Schlosser modification[93] of the Wittig reaction.

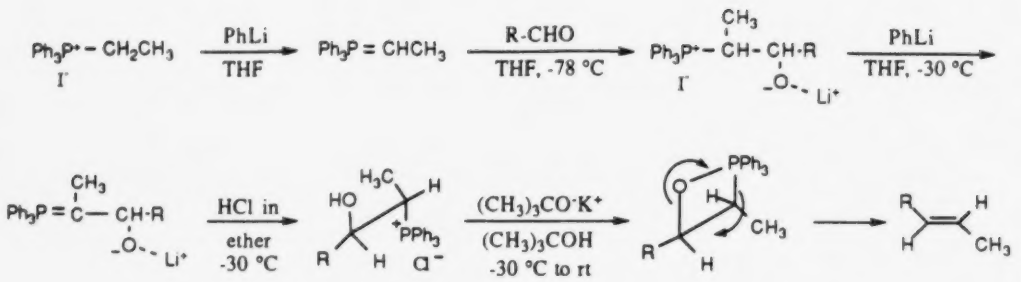
Scheme 28.



69 **71** **66**

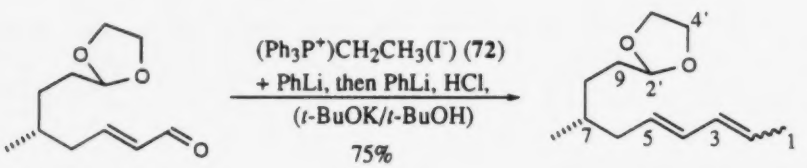
In the Wittig reaction, ylides containing stabilizing groups or those formed from trialkyphosphines generally give *E*-olefins.[94] However, ylides formed from triarylphosphines and not containing stabilizing groups often produce predominantly *Z*-olefins. Although a complete mechanism for the Wittig reaction remains to be elucidated,[95] its empirical predictability can be exploited in the synthesis of the hexaketide **50a**. The *E*:*Z* ratio of the products can often be altered by the addition of salts or by a change of solvent or reagent concentration.[96] In the Schlosser modification,[93] a strong base (phenyllithium) deprotonates the betaine-lithium iodide adduct and subsequent addition of a proton source (e.g. ethereal HCl) generates the more stable *threo*-betaine-like adduct (Scheme 29). The addition of potassium *t*-butoxide then liberates the *E*-olefin preferentially. This approach was initially attempted with unlabeled material to test its *E* to *Z* selectivity.

Scheme 29.



Use of Schlosser conditions with aldehyde **66** and phosphonium salt **72**[97] produces the 2*E*,4*E*-diene **73** with typically 5-15% of the 2*Z*,4*E*-isomer (Scheme 30). The *E*,*E* geometry of **73** is evident from the characteristic 14.2 Hz coupling constants seen between both H-2 and H-3, as well as H-4 and H-5. This mixture is difficult to separate, and is therefore best carried through to the subsequent steps.

Scheme 30.

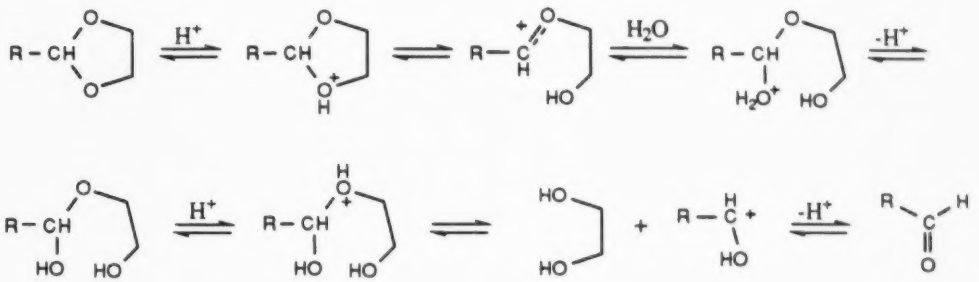


66 **73** 2*E*,4*E* : 2*Z*,4*E* 92:8

The next two steps in the overall synthesis involve the deprotection of the aldehyde and subsequent olefination to produce the third double bond, but the removal of the 1,2-ethylene glycol acetal proved difficult. Cyclic acetals (e.g. 1,3-dioxolanes) possess features that may lead them to depart from the simple hydrolysis mechanism of their acyclic analogues.[98] Although they may exhibit specific or general acid catalysis, they usually react significantly (typically 20 to 10^3-fold) more slowly than their acyclic counterparts.[99] In the initial ring-cleavage step of the hydronium catalyzed hydrolysis, the leaving group does not break away from the molecule and consequently the

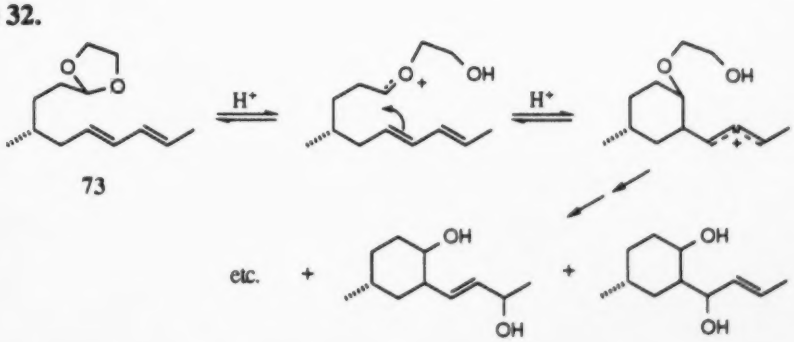
possibility exists for a reversible intramolecular attack of the alcohol hydroxyl group on the carbonium intermediate (Scheme 31). The rate-determining step may shift from the breakdown of the protonated acetal to the step involving the attack of water on the oxocarbonium ion.[100]

Scheme 31.



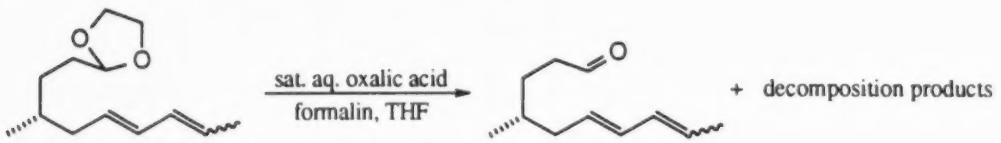
However, slow hydrolysis may not be the only problem with the dioxolane group in **73**. The diene portion of **73** could align itself such that attack by the internal olefin on the oxocarbonium ion results in a six-membered ring and a resonance-stabilized carbocation (Scheme 32). The formation of this species, which could lead to undesirable side-reactions, may be encouraged by the long reaction time of the hydrolysis. In the presence of aqueous saturated oxalic acid and THF,[101] the deprotection proceeds to 50% completion after 48 h, with TLC indicating the formation of decomposition products.

Scheme 32.



In an attempt to drive the equilibrium over to the aldehyde **74**, formalin (30% aqueous formaldehyde) was added to the reaction (Scheme 33). More aldehyde **74** is produced, but the reaction still generates decomposition products, and the isolated yield is low (50%). A potential way to circumvent this problem is to change the aldehyde protecting group to an acyclic dimethoxy acetal.

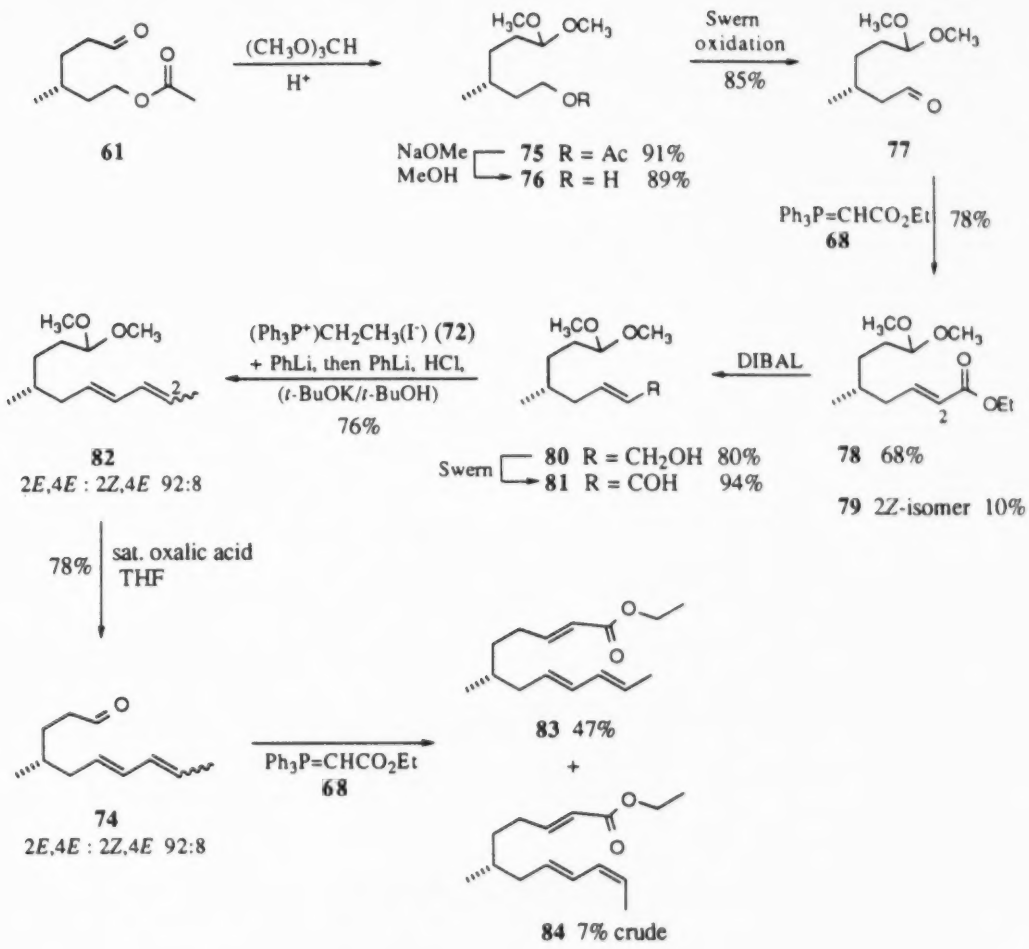
Scheme 33.



73 **74** 50%

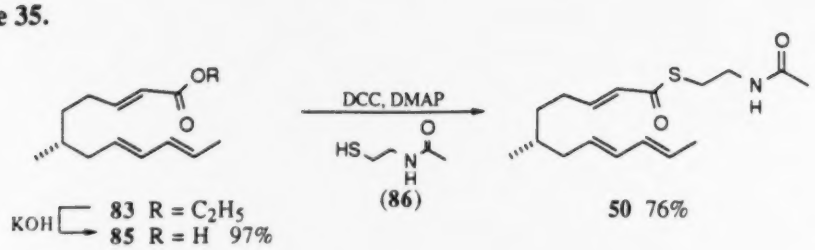
Protection[102] of aldehyde **61** with trimethyl orthoformate gives the acetal **75**, which can be converted to the protected diene **82** in a similar manner to that used to prepare **73** (Scheme 34). Saturated aqueous oxalic acid in THF[101] liberates the aldehyde **74** in 78% yield. Condensation of **74** with Wittig reagent **68** gives a mixture of triene isomers. The major *trans*-isomer **83** can be partially purified by normal flash chromatography, but it was still contaminated by the 2*E*,8*E*,10*Z*-triene **84**. This unwanted by-product, originating from *cis*-olefin formation in the Schlosser reaction, can be separated from the desired 2*E*,8*E*,10*E*-isomer **83** by MPLC with $AgNO_3$-stained silica gel.[103]

Scheme 34.



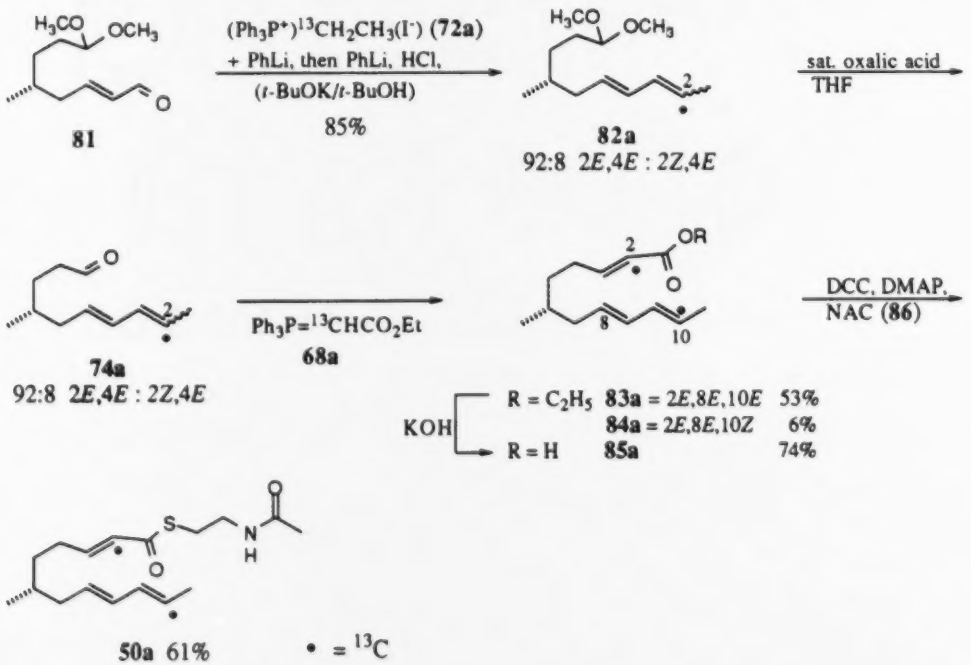
The final two steps in the overall synthesis convert the triene ethyl ester **83** to the unlabeled NAC thioester **50**. Hydrolysis[104] of the ester **83** with aqueous KOH in THF followed by simultaneous treatment[105] of the resulting acid **85** with *N*-acetyl-cysteamine **86**[106] and a mixture dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) affords the NAC ester of the hexaketide **50** (Scheme 35).

Scheme 35.



The synthetic methodology used to generate the unlabeled hexaketide **50** allows construction of the doubly-labeled *N*-acetylcysteamine derivative **50a** (Scheme 36). Reaction of the α,β-unsaturated aldehyde **81** using Schlosser-Wittig conditions with ^{13}C-labeled phosphonium iodide **72a** generates the 2*E*,4*E*-diene **82a** contaminated with 8% of the 2*Z*,4*E*-isomer. The removal of the acetal in saturated aqueous oxalic acid and THF gives the highly volatile aldehyde **74a**. It is most effective to condense this directly with the ^{13}C-labeled Wittig reagent **68a** without purification.

Scheme 36.



Purification on silver-impregnated silica gel affords essentially pure 2*E*,8*E*,10*E*-triene ethyl ester **83a** (separable from the 2*E*,8*E*,10*Z*-isomer **84a**). Hydrolysis of the ester gives the acid **85a**, and subsequent coupling to *N*-acetylcysteamine (**86**) produces the doubly-labeled NAC ester of the hexaketide **50a**.

Compound **50a** from the coupling reaction contained an impurity which showed two sets of doublets in the ^{13}C NMR spectrum at 58.6 and 33.6 ppm (J = 31.2 Hz) and 56.5 and 34.2 ppm (J = 33.2 Hz). The quantity of this material increased after normal flash chromatography and could not be removed by reverse phase HPLC. Although the ^{1}H NMR spectrum indicated only one product, it seemed that a small amount of the triene had cyclized during the reaction to form two bicyclic Diels-Alder reaction products. The two labeled carbons in each diastereomer would be adjacent giving rise to the observed two set of doublets. These bicyclic structures are of interest since an enzyme-catalyzed intramolecular cyclization may form the bicyclic system of lovastatin.

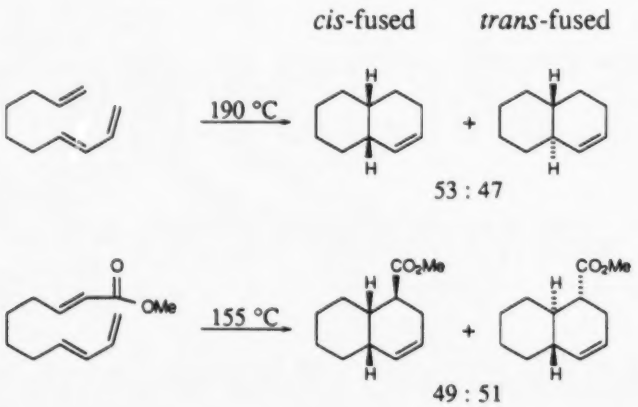
Intramolecular Diels-Alder Reactions

The intramolecular Diels-Alder reactions of 1,7,9-decatrienes forming bicyclo[4.4.0]decenes have been reviewed by several authors in the past ten years.[107] The four methylene units connecting the unsaturated centres permits the adoption of both the *exo* and *endo* transition states, leading to a mixture of *cis*- and *trans*-fused adducts. In the absence of bulky substituents, 1,7,9-decatrienes have a slight preference to form the *cis*-fused products.[107d] The activation energy is 0.3 kcal mol^{-1} higher for the formation of *trans*-fused bicyclo[4.4.0]dec-2-ene from the unsubstituted decatriene than for the *cis*-fused isomer,[108] yet Allinger's MM2 force-field approach[108,109] predicted the *trans*-fused product to be 2.0 kcal mol^{-1} more stable than the *cis*-fused product, thereby indicating that the product stability has limited use in predicting the reaction outcome. The *cis*-fused preference is not always seen experimentally because other factors such as

substituents, side chain heteroatoms, adjacent rings, and carbonyl functions can markedly alter the product distribution.[107d]

The introduction of an electron-withdrawing group such as a carboxylic ester at the dienophile terminus has been shown to have little effect on the observed stereoselectivity of the cyclization, although the reaction proceeds faster, presumably due to a lowering of the dienophile LUMO by such a functionality.[107b] Unsubstituted decatrienes show a small preference for the *cis*-fused product with the product ratio tending toward unity with increasing temperature,[108] whereas a triene with a terminal ester shows a similarly small preference for the *trans*-fused adduct (Scheme 37).[110] Secondary orbital overlap, therefore, does not play an important role in controlling the stereoselectivity during the thermal cyclizations of the trienes; this is also true in the bimolecular case where it has been observed that the *endo* selectivity decreases as the temperature of the reaction is raised.[111]

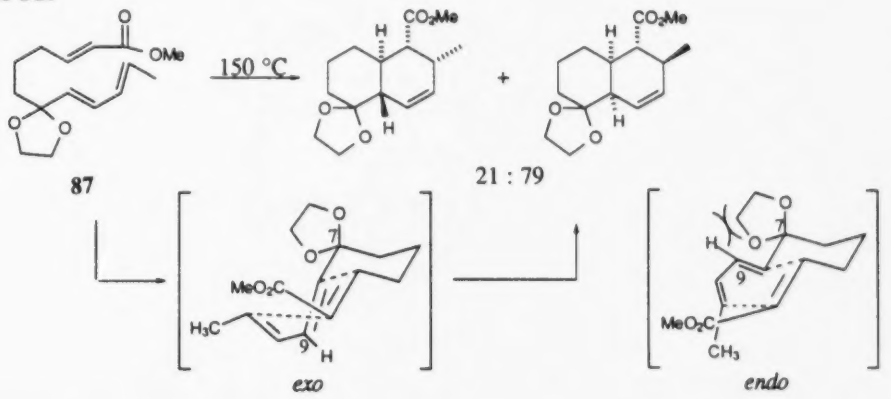
Scheme 37.



The major contributions to the stereochemical outcome seem to arise from non-bonded interactions and bond-angle strain in the Diels-Alder transition state. Six-membered rings preferentially adopt a chair conformation with substituents occupying the more stable equatorial positions. The carbon linker arm of the 1,7,9-decatrienes follows this disposition to a large degree in the conformation of their transition state.[107d] The major isomer can sometimes be predicted by comparing the *exo*

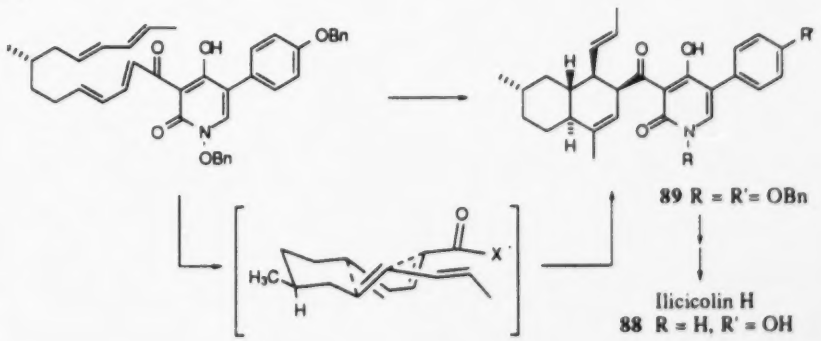
and *endo* transition states represented with the carbon connecting chain in its chair-like form; the major adduct is generated from the transition state conformation with the least bond-angle strain and fewest non-bonded interactions. Inspection of the *trans*-fused transition state (*endo*) of triene **87** reveals that an eclipsing 1,3-interaction develops between the C-9 hydrogen and C-7 alkoxy group. This interaction is absent in the *cis*-fused transition state (*exo*) and the product distribution may reflect the extent of this steric interaction (Scheme 38).[110]

Scheme 38.



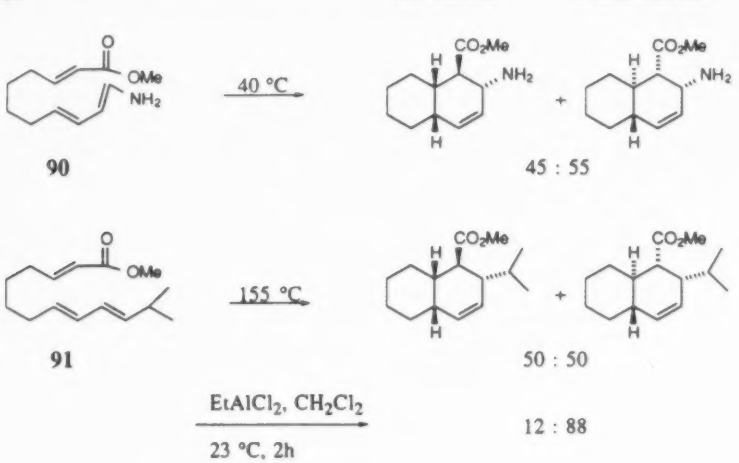
The equatorial preference of the connecting chain substituents has been exploited in the synthesis of natural products.[112,113] During the synthesis of ilicicolin H (**88**), the bicyclic *trans*-fused intermediate **89** was the exclusive product (Scheme 39).[113] It arises from a chair-like transition state with the methyl substituent having an equatorial disposition.

Scheme 39.



Involvement of secondary orbital overlap is usually observed when the temperature of the reaction can be lowered. For example, there is a slight bias toward reaction *via* the *endo* transition state exhibited by triene **90**, which generates the *trans*-fused product preferentially (Scheme 40).[114] The use of Lewis acid-catalysis has also been exploited to generate the *trans*-fused isomers preferentially from **91** (Scheme 40).[112]

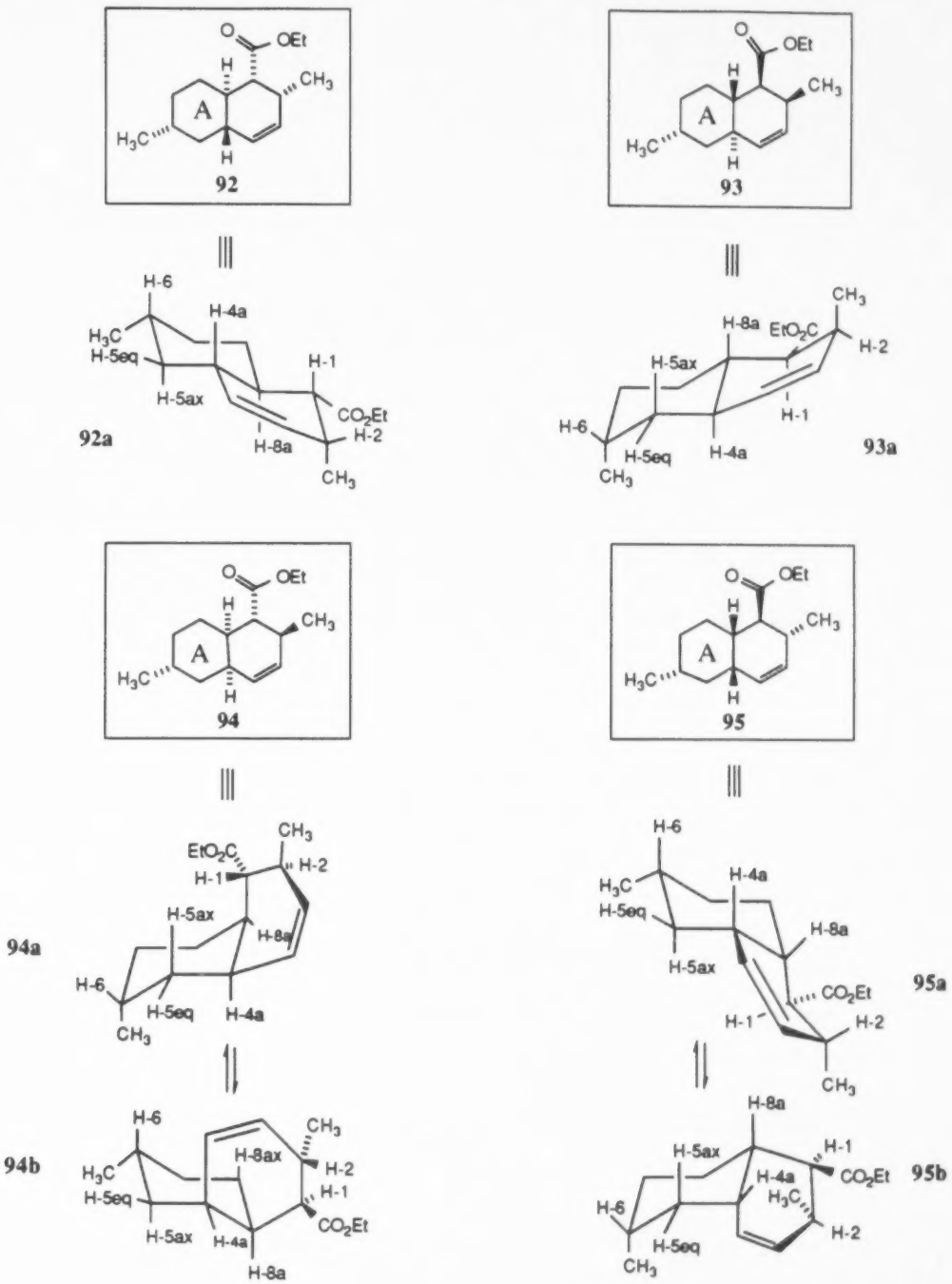
Scheme 40.



Non-enzymatic Diels-Alder Reaction of the Hexaketide

The potential stereochemical outcome of the intramolecular Diels-Alder reaction of the hexaketide ethyl ester **83** was initially considered using Dreiding molecular models. During the cyclization, the diene portion of the hexaketide **83** can react with the dienophile in an *endo* or *exo* fashion, and owing to the chiral carbon at C-6, the diene is presented with two different dienophile faces, thus leading to the formation of four possible diastereomers. The Dreiding molecular models indicate that the two possible *trans*-fused products, **92** and **93**, have restricted flexibility about the ring junction and so each exists with the A-ring (cyclohexane) in a single chair conformation represented by **92a** and **93a**, respectively (Figure 19). There is increased mobility in the potential

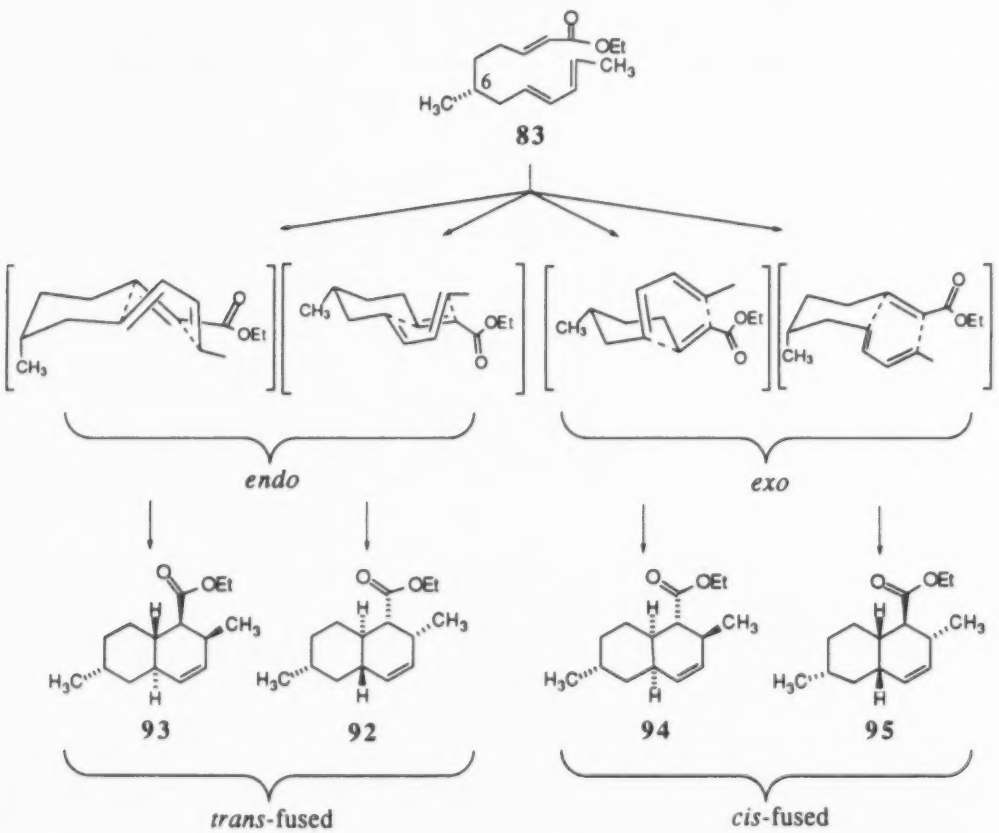
Figure 19. Possible conformations adopted by cycloadducts **92**, **93**, **94**, and **95**



cis-fused adducts, **94** and **95**, allowing the A-rings in each to adopt two possible chair conformations illustrated as **94a** and **94b**, and **95a** and **95b**, respectively.

The molecular models were also used to identify feasible transition state conformations which could be employed by the triene **83**, in which the carbon connecting chain adopts a chair-like conformation. These could be postulated as the most likely transition states. The two possible *trans*-fused products **92** and **93** could each arise from an *endo* transition state, but only one transition state leading to **92** can have the C-6 methyl group in the less sterically hindered equatorial position as suggested by the molecular models (Figure 20). An axial methyl group in the transition state would be likely to raise its energy, thus making that transition state unfavoured.

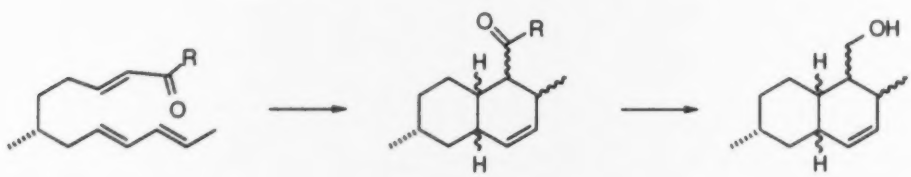
Figure 20. Four possible transition states leading to cycloadducts **92**, **93**, **94**, and **95**



A similar result is predicted for the *exo* transition states leading to the *cis*-fused adducts **94** and **95**; only the adduct **94** can be obtained from a transition state with the sterically less hindered equatorial C-6 methyl group.

In order to investigate the reactivity of the trienes under Diels-Alder conditions and the stereochemistry of the reaction products, the trienes were subjected to both thermal[110] and Lewis acid catalyzed cyclization conditions.[110] A solution of the triene ethyl ester **83** in toluene heated to 160 °C for 4 days in a sealed tube generates a 1:1 mixture of **96** and **97** (72%), separable by flash chromatography, along with a small amount (6%) of unreacted starting material **83** (Figure 21). The free acid triene **85** and NAC ester triene **50** also cyclize under the thermal conditions and produce 1:1 mixtures of cycloadducts **98** and **99** (83%), and **100** and **101** (81%), respectively. Both mixtures are difficult to separate. The two cyclized ethyl esters **96** and **97** were reduced[115] to their corresponding alcohols **102** (80%) and **103** (86%), respectively, with lithium aluminium hydride. The two mixtures of cyclized products from the NAC ester **50** and free acid **85** reactions were also reduced to their alcohols (79% & 81%, respectively).

Figure 21. Compounds generated from thermal Diels-Alder reactions



83 R = OEt
85 R = OH
50 R = $S(CH_2)_2NHAc$

96 and 97 R = OEt
98 and 99 R = OH
100 and 101 R = $S(CH_2)_2NHAc$

102 and 103

A comparison of the ^1H NMR data of the alcohols **102** and **103**, generated from each ethyl ester reduction, with the mixture of alcohols from the NAC ester and free acid reductions demonstrates that each of the Diels-Alder reactions (of **83**, **85**, and **50**) has the same stereochemical outcome and produces two analogous products. To examine the

effects of a Lewis acid on the cyclization, both the ethyl **83** and NAC esters **50** were treated with 0.9 equivalents of ethylaluminum dichloride ($EtAlCl_2$) at room temperature. Each reaction was complete in less than 3 h. Each ester generates the same two cycloadducts as produced from their respective thermal reactions, except the product mixtures are no longer in a 1:1 ratio. The ethyl ester delivers a 9:1 mixture of **96**:**97** (58%) and the NAC ester affords **100**:**101** (80%) in a ratio of 19:1. Although the same two products result from the thermal reaction, the Lewis acid cyclizations proceed rapidly at room temperature and show significant product selectivity.

The stereochemical assignments of the cycloadducts required combined use of ^1H, ^{13}C, COSY, HMQC, and ^1H-decoupled NMR experiments. The higher R_f diastereomer **96** from the triene ethyl ester cyclization was examined first. The connectivity of the proton coupling in the ^1H COSY spectrum, shown in Figure 22 (next page), allows complete assignment of the ^1H signals, and irradiation experiments show a characteristic *trans*-fused coupling constant of 12.0 Hz between H-8a and H-4a, thus eliminating the two potential *cis*-fused adducts as possible structures. The distinction between the two *trans*-fused adducts, **92** and **93**, is based upon the coupling pattern seen for H-5ax. In the two most probable conformations for the *trans*-fused products, only the **92a** conformer allows for an axial-axial arrangement between H-5ax and H-4a, and H-5ax and H-6 (Figure 23).

Figure 23. Structural comparison of *trans*-fused products **92a** with **93a**

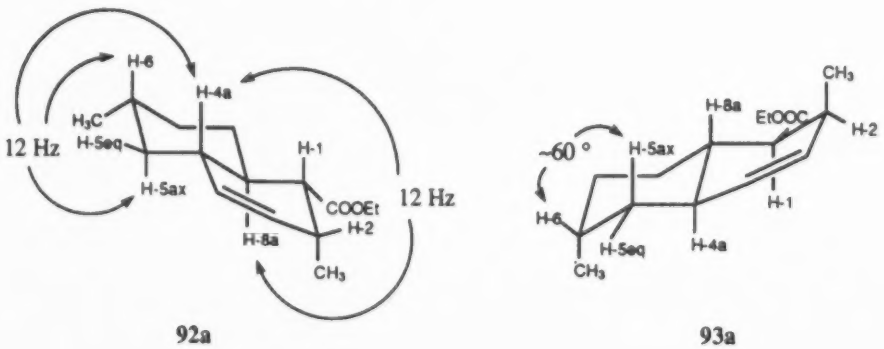
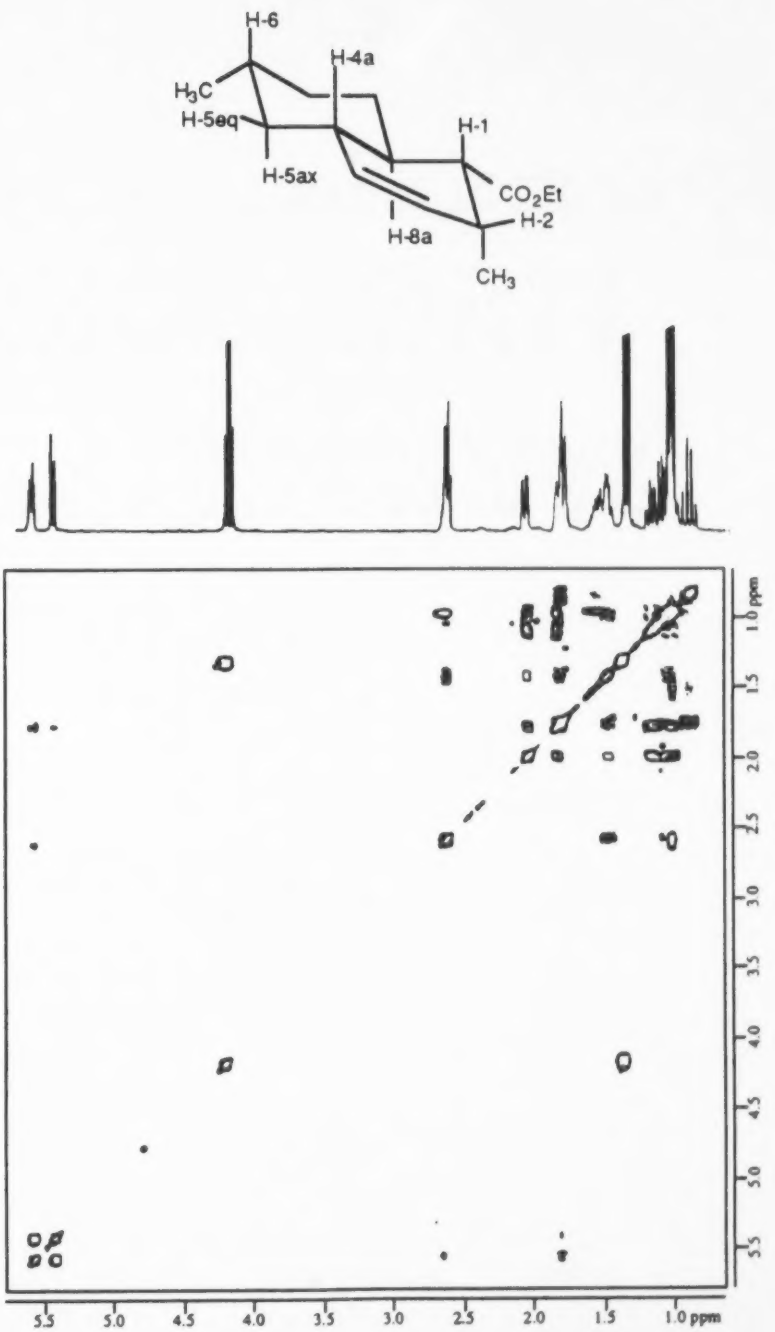


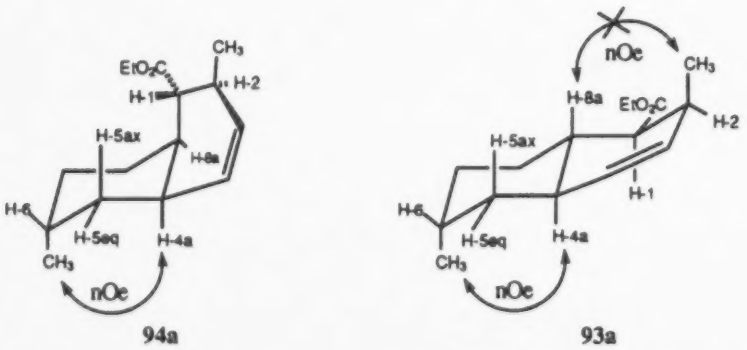
Figure 22. COSY NMR spectrum and structure of cycloadduct **92** & **96**



The multiplicity of the H-5ax signal is an apparent quartet arising from three doublets each having a coupling constant of 12.0 Hz. Two of the three doublets are a result from the two axial-axial vicinal couplings and the third from the geminal coupling with H-5eq. Hence, the *trans*-fused adduct **92**, which has the opposite stereochemistry on ring B (cyclohexene) as lovastatin (**5**), is one of the two diastereomers produced in the Diels-Alder reaction.

The ^{1}H and ^{13}C signals of the second cyclized compound **97** were fully assigned using similar NMR techniques. The stereochemical elucidation is hindered by the complexity of the fused-ring proton signals since the magnitude of the coupling constant between H-4a and H-8a can not be measured easily. Lacking this value, there are still three possible structures (**93**, **94**, and **95**). The difference ^{1}H nOe spectra in which the overlapping C-6 and C-2 methyl protons are irradiated, show an enhancement of the H-4a and not the H-8a signal, which clearly eliminates the *cis*-fused product **95** as a possible structure, since no conformation of this isomer would allow an nOe enhancement between the H-4a and H-8a and the bicyclic methyl substituents. This enhancement indicates the *cis*-fused conformer **94a** as the most likely structure, since there is only an enhancement at H-4a. However, the single enhancement could correspond to the *trans*-fused product **93a** if the C-2 methyl group is bent away from the H-8a hydrogen (Figure 24).

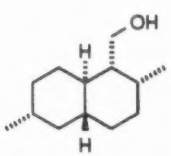
Figure 24. Cycloadduct conformations and observed nOe enhancements



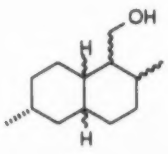
The magnitude of the coupling constant between the ring-fused protons could not be determined for the NAC ester **101**, free acid **99** or alcohol **103** cyclized products. Hydrogenation[116] of the alcohols **102** and **103** proceeds readily to the corresponding decalins **104** (65%) and **105** (28%), respectively (Figure 25), but the aliphatic region becomes very complex because of signal overlap. Even though the nOe evidence suggests the *cis*-fused product **94** as the second diastereomer in the non-enzymatic Diels-Alder reaction, the possible formation of the *trans*-fused product **93** could not at this stage be unequivocally ruled eliminated.

Another approach was attempted to ascertain the stereochemistry of the second Diels-Alder product. The *p*-bromophenyl esters **106** and **107** were prepared[117] from the 1:1 mixture of cyclized free acids **98** and **99** in the hope that the esters would be suitable candidates for x-ray crystal structure analysis (Figure 25). The reaction produces a mixture of esters **106** and **107** (62%), which is difficult to separate and neither diastereomer can be selectively crystallized from the mixture.

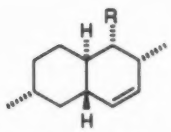
Figure 25. Derivatives of the cycloadducts



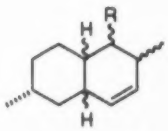
104



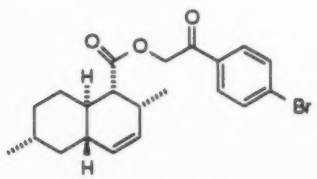
105



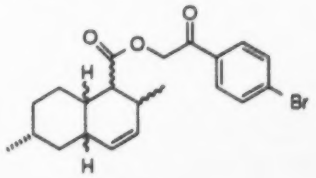
102 R = CH_2OH
98 R = COOH
100 R = $COS(CH_2)_2NHAc$



103 R = CH_2OH
99 R = COOH
101 R = $COS(CH_2)_2NHAc$



106



107

The full assignment of the ^{1}H and ^{13}C signals for both diastereomers, **106** and **107**, is aided by the synthesis of diastereomerically pure *p*-bromophenyl ester **106**. The alcohol **102** derived from the higher R_f ethyl ester **96** was oxidized[118] to the acid **98** (51%), and protected as the *p*-bromophenyl ester **106** (40%). The NMR assignments for the second product **107** were made by comparing the NMR spectra of the mixture with the NMR spectral data for the independently prepared ester **106**. This comparative method also permits a full spectral assignment of the 1:1 mixture of the NAC ester and free acid cycloadducts because the pure NAC ester **100** and free acid **98** could be obtained.

The stereochemistry of the potential *trans*-fused product **93** is identical to that seen in the bicyclic core of 4a,5-dihydrolovastatin (**8**). The independent synthesis of **93** as a reference compound would allow for the absolute stereochemical determination of the last Diels-Alder product. The NMR data of **93** could be compared with those of **97**, thus confirming or eliminating **93** as a possible product. Compound **93** contains the decalin system formed after the postulated enzyme-catalyzed Diels-Alder reaction. Once the synthetic route to this compound has been established, labeled **93** or chain-extended precursors can be constructed and be used as further probes in the elucidation of lovastatin's biosynthetic pathway.

Synthesis of Bicyclic Reference Compound 93

The total synthesis of dihydrolovastatin (4a,5-dihydromonacolin L (**8**)) represents a challenge that has been undertaken by many research groups,[119] but the most efficient route to the desired reference compound **93** utilizes the methodology devised by Lewis and coworkers.[119e] It appeared that the tricyclic lactone **108** generated during this literature synthesis would be an ideal starting material, since it contains the required stereochemistry and the only modification required would be the removal of the lactone from the A-ring (Figure 26).

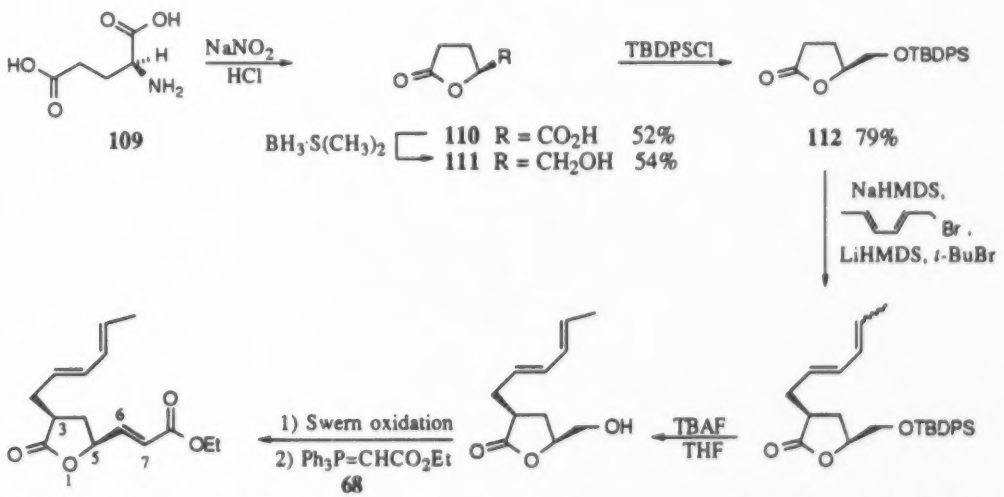
Figure 26. Formation of the reference compound **93**

Tricyclic lactone
108

Reference compound
93

The tricyclic lactone **108** was synthesized using published literature procedures.[119e,120] Diazotization and lactonization of commercially available L-glutamic acid (**109**) gives the carboxylic acid lactone **110** with complete retention of configuration (Scheme 41).[120] Reduction of the acid **110** generates the alcohol **111**, which is readily protected as its diphenyl *tert*-butyl silyl ether **112**.

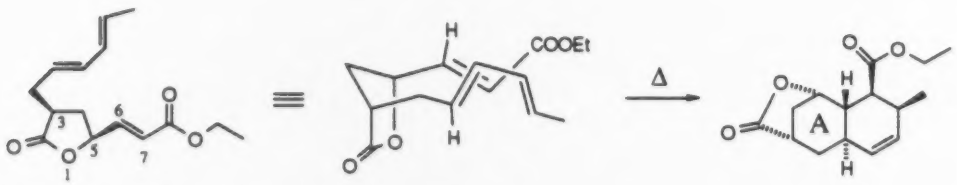
Scheme 41.



The enolate of the protected butyrolactone **112** can be alkylated with hexa-2,4-dienyl bromide[121] and then re-enolized and protonated from the less hindered face of the enolate using the bulky *tert*-butyl bromide as the proton source. This yields the two possible diastereomers **113** and **114** in a syn:anti ratio of approximately 4:1 along with some dialkylated material **115**. All of the alkylated products contain 8% of an *E,Z*-isomer, which is formed during the generation of the hexa-2,4-dienyl bromide from hexadienyl alcohol. The diastereomers **113** and **114** are separable by chromatography. Deprotection of the major isomer **113** gives the alcohol **116**, which can be recrystallized to diastereomeric purity (ie. removal of the *E,Z*-diene impurity). Swern oxidation of the alcohol **116** and trapping of the aldehyde *in situ* with the stabilized Wittig reagent **68** affords the all *E*-triene **117** as the major product. This procedure also generates the *Z*-olefin **119** and the anti-triene **118**, which results from epimerization of the intermediate aldehyde at C-5.

The five-membered lactone ring controls the flexibility of the triene **117** such that the reacting conformer seems to be **117a** leading to the desired isomer **108** (Figure 27). The triene **117** is thermally cyclized to yield the functionalized decalin **108**, which has the correct stereochemistry at the six chiral centres. The reaction is complete after 11 days in refluxing mesitylene (48%) or 5 days in toluene in a sealed tube at 160 °C (60%).[122]

Figure 27. Conformation of the triene **117** controlling the Diels-Alder reaction



117 (3*S*,5*S*)-*E,E,E*-isomer

117a
endo

108
trans-fused

Attempts to shorten the reactions times using Lewis acid catalysis (0.95 to 5.0 equivalents of $EtAlCl_2$) and various temperatures (25 °C to 120 °C) failed and only decomposition products or starting material were observed.

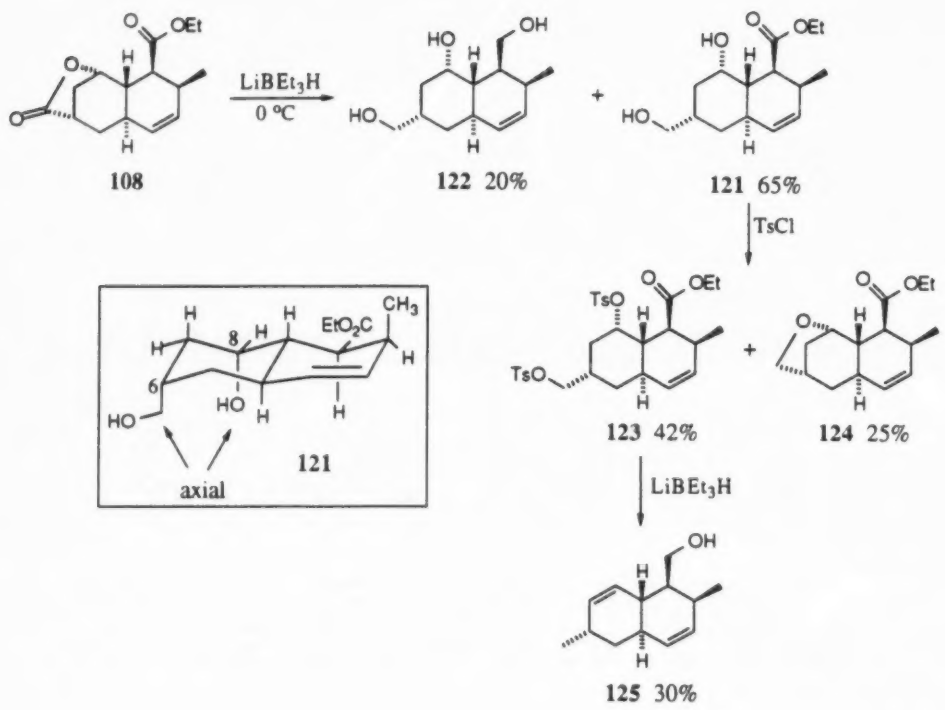
The preparation of the reference compound **93** from the tricyclic lactone **108** initially seems to be a straightforward matter of reduction of the lactone to a diol, followed by tosylation and elimination of both tosylates.[123] This should produce the reference material as its alcohol **120** which could be compared to the Diels-Alder adducts after the ester reductions to their corresponding alcohols (Scheme 42).

Scheme 42.

108 **120**

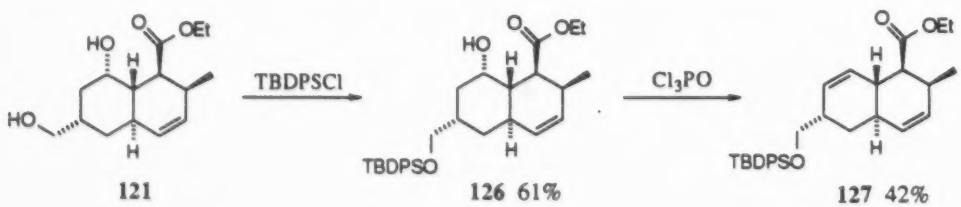
Reduction of the lactone **108** with lithium triethylborohydride generates the diol **121** and the triol **122** (Scheme 43). During the tosylation of the diol **121** to the ditosylate **123**, the tricyclic ether **124** forms in 25% yield, indicating for the first time that the axial hydroxyl group at C-8 could present a problem because of its juxtaposition with the axial methylene group at C-6. Treatment of the ditosylate **123** with lithium aluminium hydride or super hydride displaces the primary tosylate, but also eliminates the secondary tosylate to generate the diene **125**. The anti-periplanar relationship between the activated alcohol at C-8 and the vicinal hydrogens means that elimination to the olefin is facile.

Scheme 43.



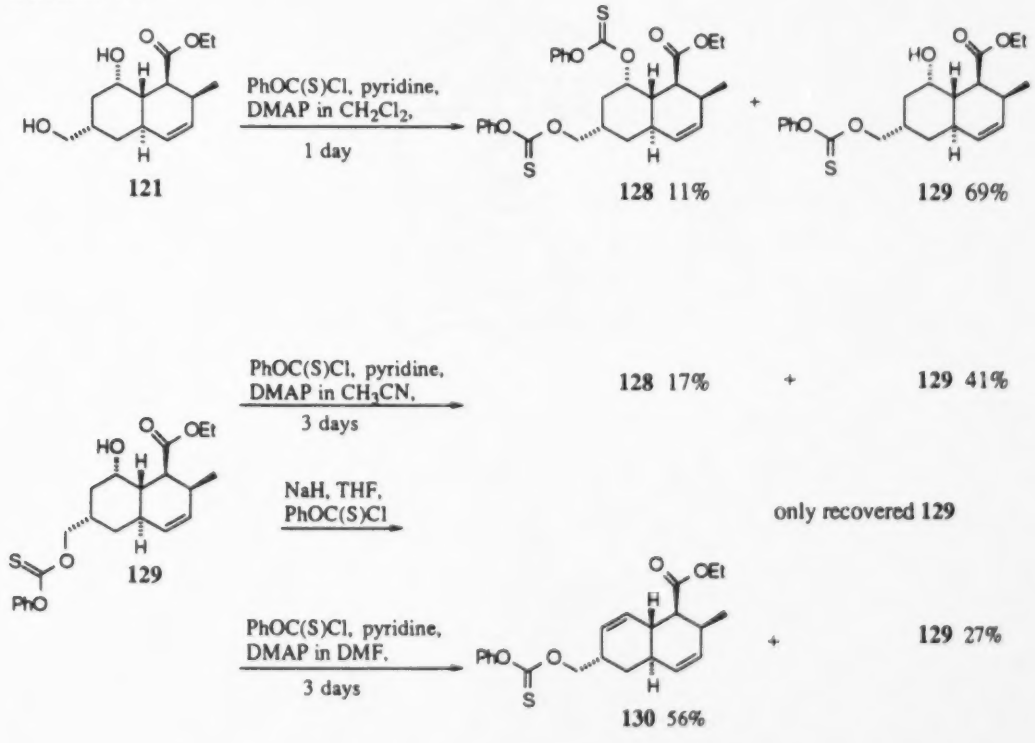
To suppress the elimination pathway, attempts were made to invert the substituent at C-8 into the equatorial position. However, Mitsunobu inversion conditions[75] give no reaction and halogenation[124] of the primary TBDPS-protected alcohol **126** with either thionyl chloride or phosphorous oxychloride produces only the elimination product **127** (Scheme 44). It seemed that an ionic approach to remove the hydroxyl groups was inappropriate, so radical methodology based on Barton deoxygenation chemistry was undertaken.[125]

Scheme 44.



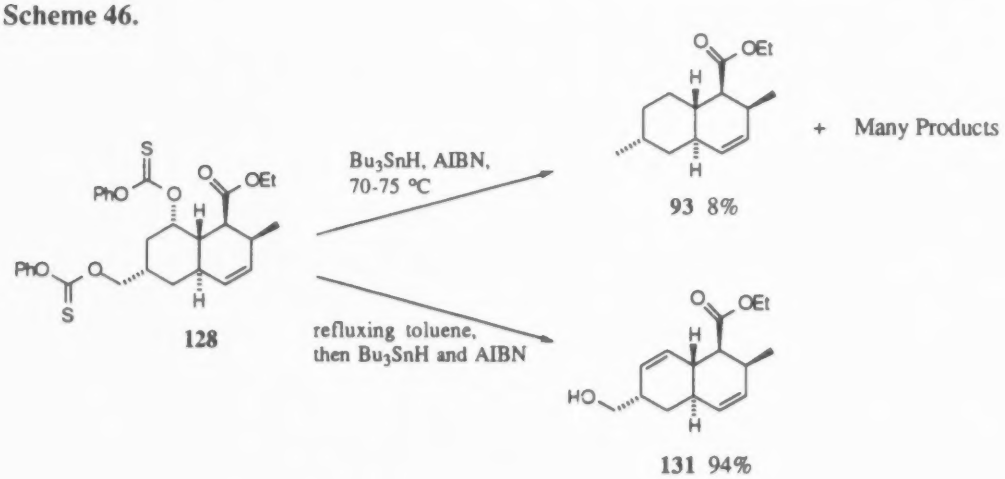
Potentially homolytic cleavage of both C-O bonds in the diol **121** could be performed in one step. After protection of the hydroxyl groups with a suitable thiocarbonyl compound, the resultant material could be treated with tri-*n*-butyltin hydride to deliver the reference compound **93**. The first activating moiety used was the phenoxythiocarbonyl group.[126] Thus, reaction of the diol **121** with phenoxythiocarbonyl chloride generates a mixture of the di- and mono-thionocarbonates, **128** and **129** respectively (Scheme 45). Since the desired *bis*-activated compound **128** forms in low yield, a second acylation of the mono-protected product **129** was attempted under various conditions to complete the conversion. Reaction in DMF produces the elimination product **130**, whereas reaction in acetonitrile gives only low yield of **128**. Initial treatment of **129** with sodium hydride, followed by phenoxythiocarbonyl chloride leads to unreacted starting material **129**. The low or no yields of **128** are possibly due to the steric bulk of the primary protecting group blocking the secondary axial hydroxyl group.

Scheme 45.



Deoxygenation of the *bis*-phenyl thionocarbonate ester **128** with tri-*n*-butyltin hydride, initiated by AIBN, gives the desired decalin ester **93** in low yield along with many other products as indicated by TLC (Scheme 46). Barton has noted that the use of tri-*n*-butyltin hydride instead of triphenyltin hydride with slow addition of the stannane to the thiocarbonyl derivative improves the yields for primary alcohol deoxygenations.[127] Implementing these conditions deprotects the primary alcohol and causes olefin formation in the A-ring to furnish **131**. Since the synthetic pathway to the reference material **93** could be utilized in the production of labeled material to aid in the elucidation of lovastatin biosynthesis, the combined low yield (< 1%) of these two reactions to **93** preclude their use in an efficient synthesis.

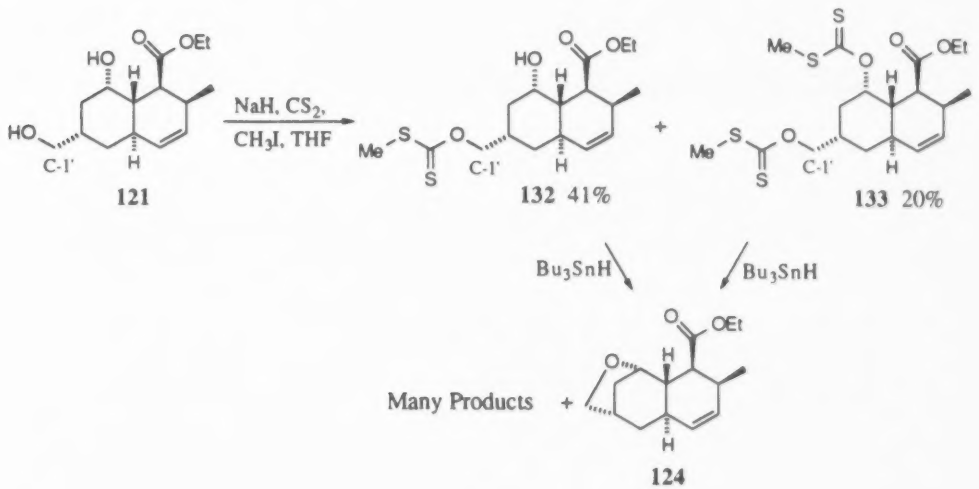
Scheme 46.



Methyl xanthates are potential alternative thiocarbonyl activating groups. In the presence of NaH, followed by sequential addition of carbon disulfide and methyl iodide,[128] the diol **121** affords both the mono **132** and the diprotected alcohol **133** (Scheme 47). The removal of the methyl xanthate groups from either material is difficult. Treatment of either **132** or **133** with tri-*n*-butyltin hydride forms many products, with a high preponderance of the tricyclic ether **124**. In the reaction with **133**, this could result

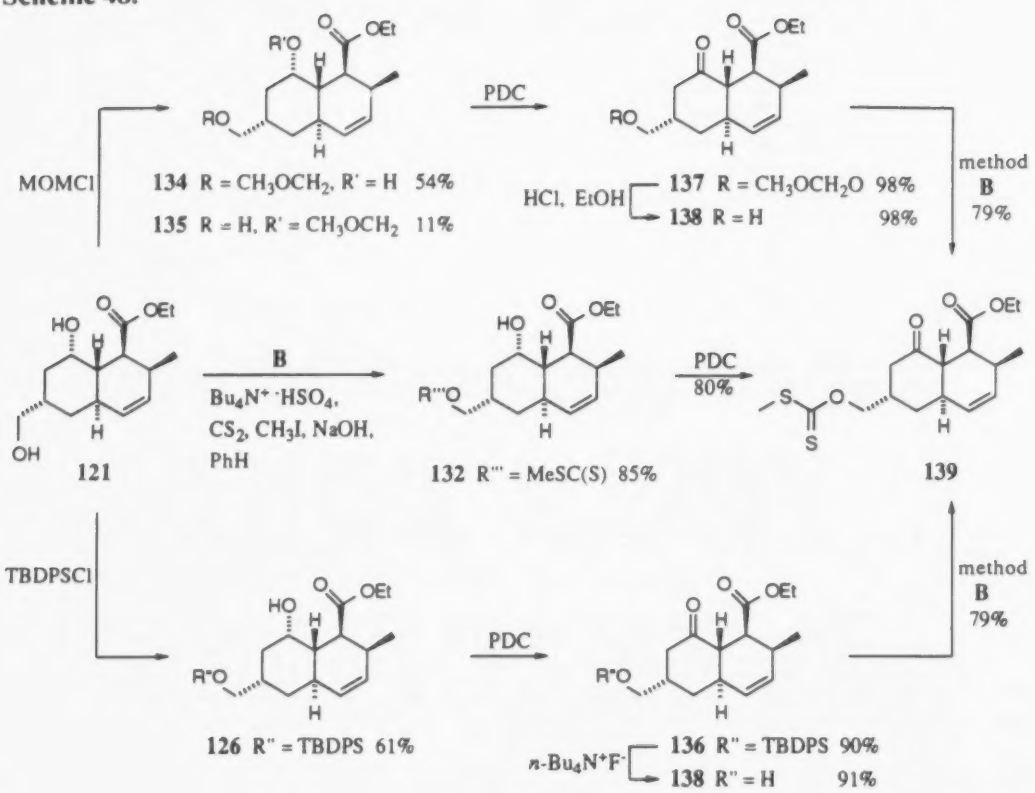
from C-8 hydroxyl group deprotection, followed by displacement of the protecting group at C-1'. For the mono-protected alcohol **132**, straight displacement would generate the tricyclic ether **124**.

Scheme 47.



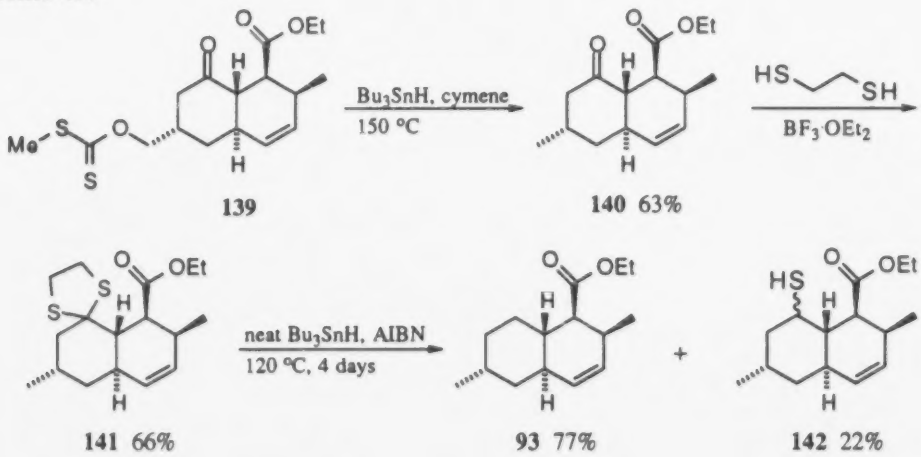
The interference caused by the C-8 hydroxyl group could be circumvented by oxidation to the corresponding ketone (Scheme 48). The silyl ether **126** or methoxymethyl ether **134**, derived from diol **121**, are oxidized[129] by pyridinium dichromate (PDC) to the corresponding ketones **136** or **137**, respectively. Removal of the protecting groups from **136** and **137** in each case generates the hydroxyketone **138**. Reaction of this compound in a two phase system[130] of tetrabutylammonium hydrogen sulfate in 4N NaOH and benzene, followed by the addition of carbon disulfide and methyl iodide gives the methyl xanthate **139**. An alternative sequence generates the primary methyl xanthate **132** *via* the two phase system and direct oxidation to the ketone **139**.

Scheme 48.



Deoxygenation[127] of the methyl xanthate **139** occurs at 150 °C to produce the keto-ester **140**, which is subsequently protected[131] as the dithioketal **141** (Scheme 49).

Scheme 49.

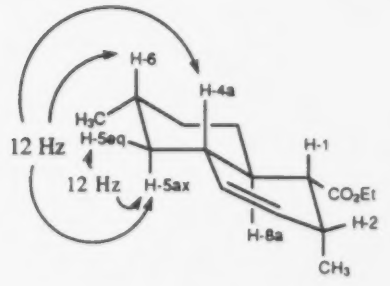


Attempts to remove the ketal with Raney-nickel[132] were unsuccessful. Activated Raney-nickel causes over-reaction and generates highly saturated compounds. Full or partial deactivation of the reagent leads to either a mixture of products or isolation of starting material. However, reaction of the dithioketal **141** in neat tri-*n*-butyltin hydride and catalytic AIBN at elevated temperatures[133] produces the desired reference compound **93** in good yield along with a partially-reduced species **142**, which could be converted into **93** by further reaction.

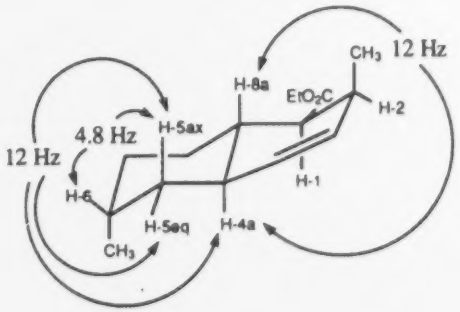
The ^{1}H and ^{13}C signals of the reference compound **93**, assigned using 1-D and 2-D NMR experiments, were compared with the those from the unknown structure **97** in the Diels-Alder reaction of the triene ethyl ester **83**. The completely different spectral data illustrate that the second product from the intramolecular cyclization is *cis*-fused structure **94** (ie. **94** = **97**) (Figure 28, next page). An example of the NMR spectral dissimilarity is illustrated by the difference between the ^{1}H COSY spectra of **94** and **93** seen in Figures 28 and 29, respectively.

The ^{1}H NMR coupling constants verify the structure of **93**. The two large coupling constants for the ring-fused proton H-4a suggest a 180° relationship between CH-4a and CH-5ax, and CH-4a and CH-8a (Figure 30). The H-5ax coupling constants can be compared with those in the first Diels-Alder product **92**.

Figure 30. Large vicinal coupling in cycloadducts **92a** and **93a**



92a



93a

Figure 28. COSY NMR spectrum and structure of cycloadduct **94** & **97**

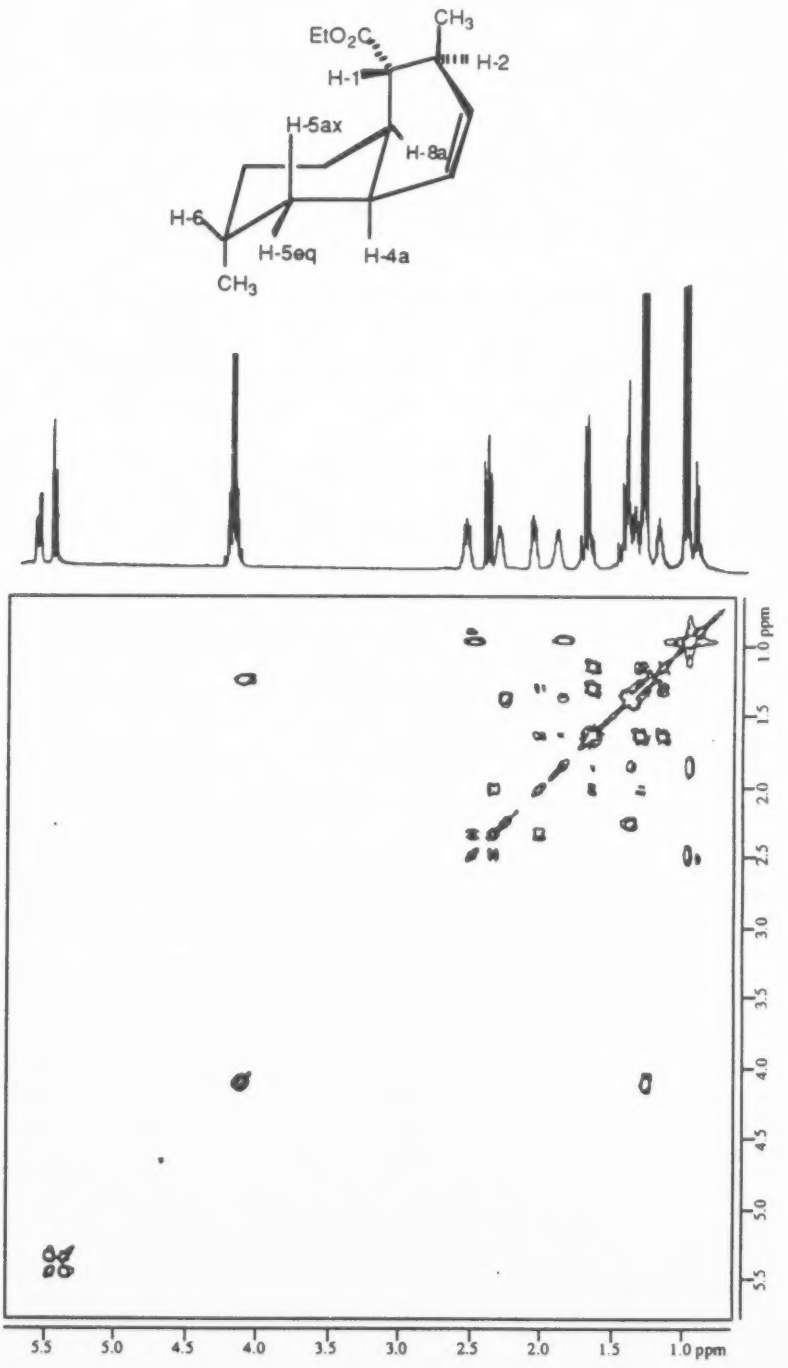
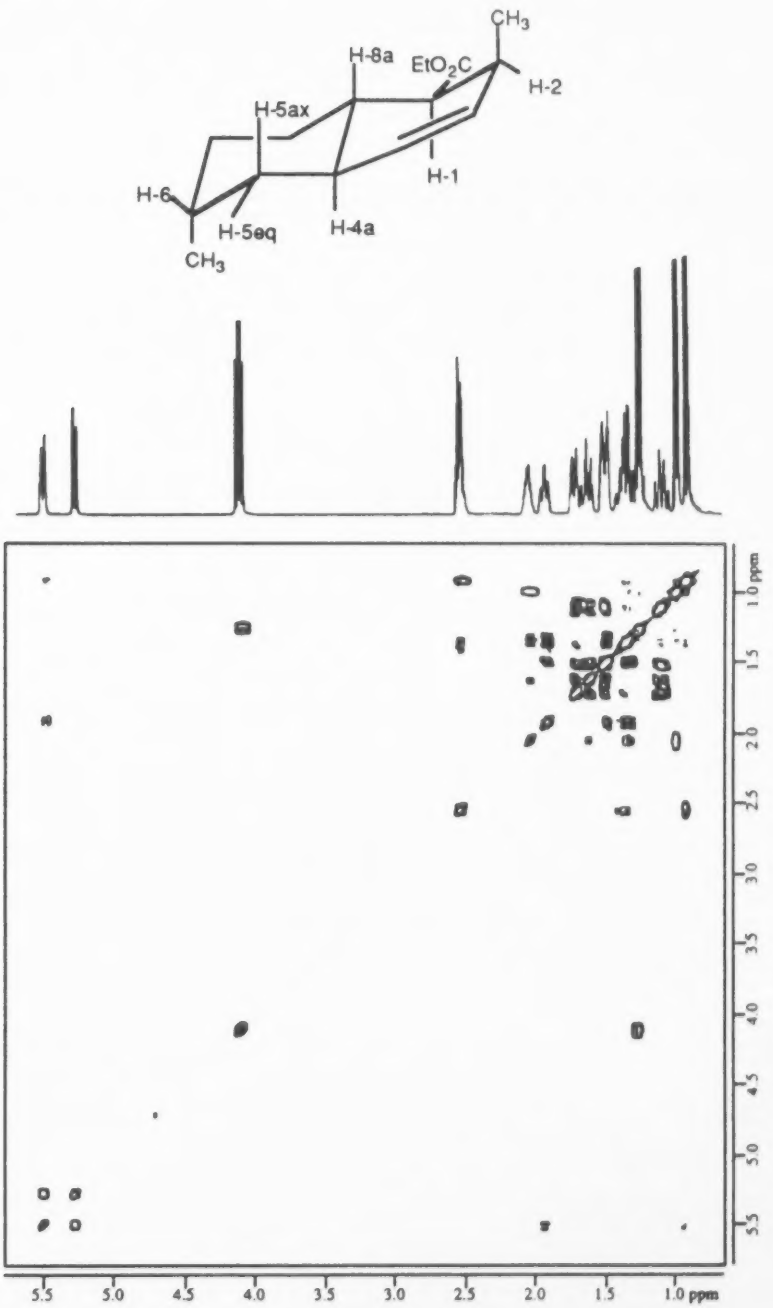


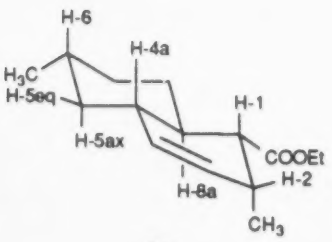
Figure 29. COSY NMR spectrum and structure of cycloadduct **93**



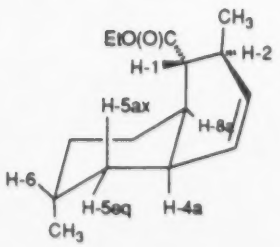
As previously mentioned, the H-5ax proton in **92** could assume an axial-axial relationship with both H-4a and H-6 and has geminal coupling with H-5eq. The multiplicity for this signal is the expected three doublets, each having a large coupling constant. The peak for the H-5ax proton in **93a**, however, contains only two large coupling constants corresponding to the axial-axial relationship of H-5ax and H-4a and the geminal coupling with H-5eq. The third doublet in this signal shows only a 4.8 Hz coupling constant between H-5ax and H-6.

Since the Diels-Alder reaction of the triene ethyl ester **83** yields the *trans*-fused product **92** and the *cis*-fused product **94**, and since the analogous diastereomers are produced by cyclization of triene acid **85** and triene thioester **50**, the stereochemistry in all the previously synthesized bicyclic compounds can be determined (Figure 31). The rigidity of the *trans*-fused ring junction holds **92** in a conformation such that the C-6 methyl group is equatorial (**92a**), but the *cis*-fused adduct **94** has a solution conformation with an axial C-6 methyl substituent (**94a**).

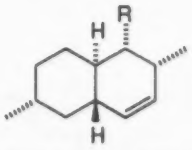
Figure 31. Stereochemistry of the Diels-Alder products and derivatives



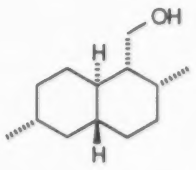
92a



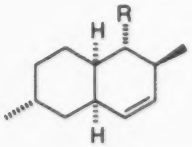
94a



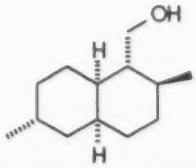
92 & 96 R = COOEt
102 R = CH_2OH
98 R = COOH
100 R = $COS(CH_2)_2NHAc$
106 R = $COOCH_2COC_6H_5Br$



104



94 & 97 R = COOEt
103 R = CH_2OH
99 R = COOH
101 R = $COS(CH_2)_2NHAc$
107 R = $COOCH_2COC_6H_5Br$



105

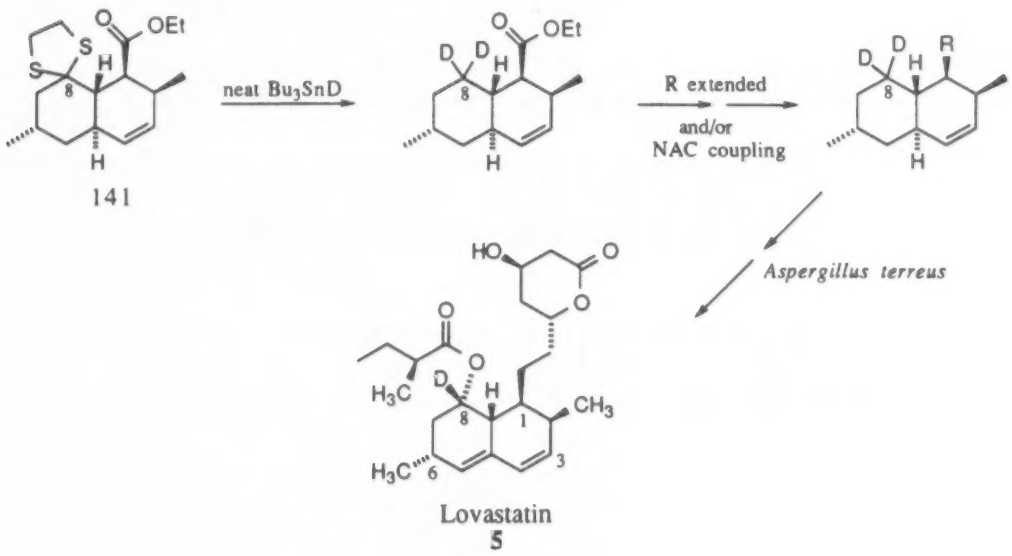
As previously mentioned, Dreiding models of the acyclic material suggest transition states for each of the two *trans* -fused products with the A-ring adopting a chair-like conformation. The generation of **92** rather than **93** in the non-enzymatic reactions, could be due to a preference for the methyl group occupying the more favorable equatorial position (Figure 20). The *cis*-fused product **94** could also form through a transition state with an equatorial C-6 methyl group, and after cyclization it could flip to the conformer **94a** with the methyl group in the axial position (Figure 20). In the presence of the Lewis acid, the observed *trans*- over *cis*-fused adduct preference could result from involvement of secondary orbital overlap.

The reference compound **93**, containing the same stereochemistry in the bicyclic ring as 4a,5-dihydromonacolin L (**8**), is not produced in the non-enzymatic cyclization reaction. If the labeled hexaketide **50a** is incorporated into lovastatin (**5**) after inoculation and fermentation, the above findings lend support to the existence of a cyclase enzyme. From the observed product distribution in the ethyl ester reaction, one could assume that the transition state leading to **93** is of higher energy than those leading to **92** and **94**. The presence of an enzyme in the biological system could lower the energy of this transition state possibly through steric constraints within the active site, thus allowing for cyclization of the required diastereomer.

In addition to providing a key reference compound, the synthesis of the bicyclic compound **93** affords a synthetic route to labeled precursors useful for biosynthetic investigations. In the biosynthesis of lovastatin (**5**), the acyclic hexaketide triene is probably cyclized and processed on the polyketide synthase complex. To determine the sequence of further transformations, a label can be affixed during the synthesis of the reference compound **93**. This can then be converted to the NAC-ester before or after further chain extension. An example of such a synthesis is shown in Scheme 50, where the reduction of the dithioketal **141** in the presence of tri-*n*-butyl deuteride results in incorporation of two deuterium atoms on the C-8 carbon. The resultant NAC coupled

products could be used as probes for the later stages of lovastatin biosynthesis by addition to *Aspergillus terreus* culture media and observation of the deuterium incorporation in the isolated metabolite.

Scheme 50.



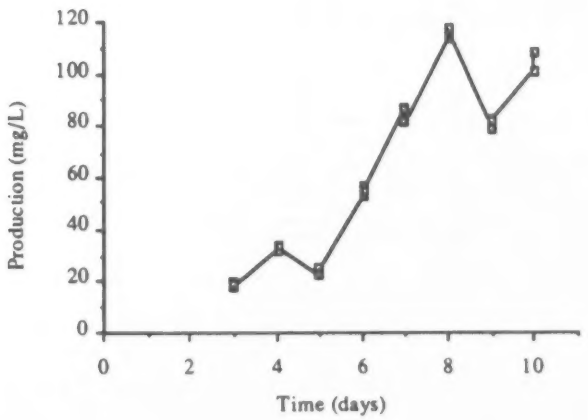
Production of Lovastatin and β-Oxidation Inhibition

The original fungal strain of *Aspergillus terreus* ATCC 20542 used in our research group was plagued with a declining production of lovastatin (**5**), which hindered the elucidation of the source of oxygen atoms in the metabolite **5**. The incorporation of ^{13}C-labeled precursors into secondary metabolites is often low (commonly 1.0 % or less), therefore it is necessary that a sufficient amount of metabolite be produced for detection of the label in the ^{13}C NMR spectrum. Prior to the incorporation studies with the hexaketide **50a**, the production of lovastatin from a new fungal strain of *Aspergillus terreus*, MF 4845, had to be confirmed and elevated to suitable levels for detectable

incorporations. The *A. terreus* MF 4845 was grown under a variety of conditions to optimize the production of lovastatin.

The conditions for the original strain ATCC 20542 employed a two stage fermentation process.[33] The fungal mycelium grown from spores in the growth medium was transferred in small aliquots to several flasks containing the production medium. This medium contained the nutrients necessary for full fungal development and secondary metabolite generation. The new fungal strain, MF 4845, was tested in the original fermentation media along with combinations of different growth and production media. A combination was found that consistently produced lovastatin in concentrations greater than 120 mg/L, a respectable quantity for incorporation studies . The production curve of lovastatin was constructed by daily isolation of the metabolite from the fermentation medium and quantification by HLPC (Figure 32). The yield of lovastatin reached a maximum after about 8 days.

Figure 32. Production curve of lovastatin (**5**) by *Aspergillus terreus* MF 4845



A major problem encountered with attempted loading of advanced putative intermediates onto the polyketide synthase is the competitive degradation of these compounds by highly efficient β-oxidation enzymes. β-Oxidation enzymes can cleave

the labeled precursors into small carboxylic acid moieties before their incorporation into the metabolite, thus severely decreasing the amount of intact utilization.[8-13] The overall process of β-oxidation, a common pathway for the metabolism of fatty acids, occurs in a cycle of four distinct steps:

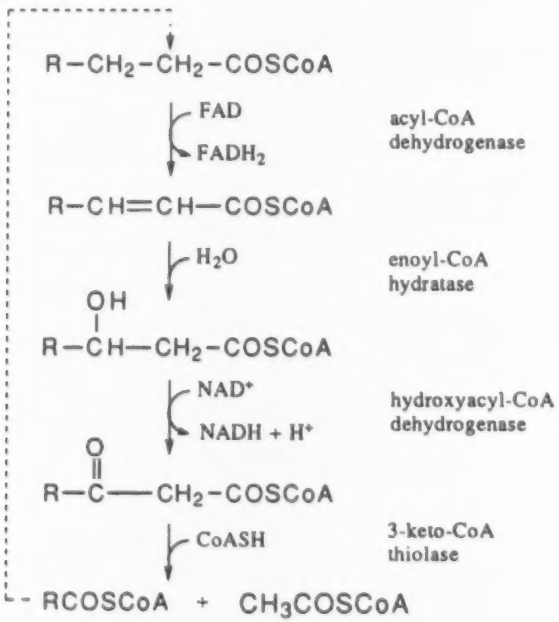
(1) Dehydrogenation of the fatty acid CoA ester to the *trans*-enoyl-CoA[134-137]

(2) Hydration to 3-hydroxyacyl-CoA[138,139]

(3) Dehydrogenation to 3-ketoacyl-CoA[138,139]

(4) Thiolytic cleavage of the 3-ketoacyl-CoA thioester to an acyl-CoA chain shortened by two carbon atoms and acetyl-CoA (Scheme 51).

Scheme 51.

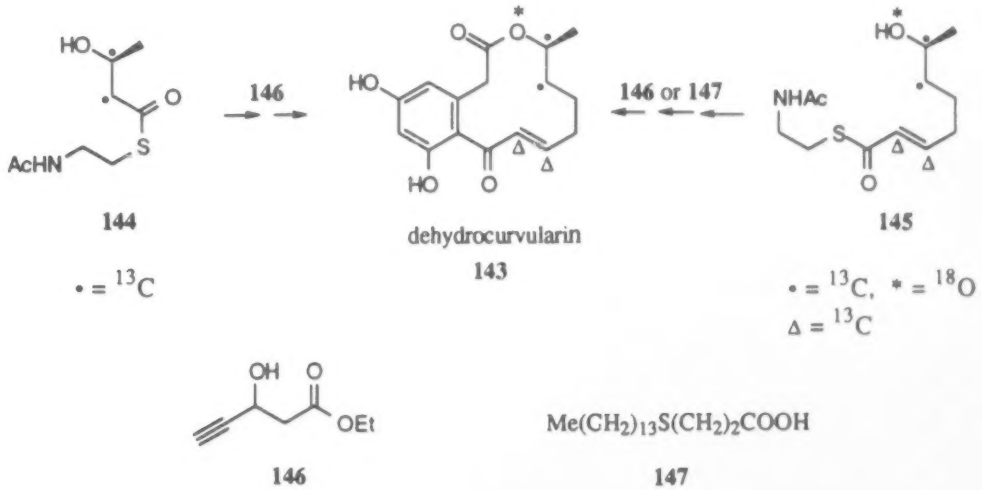


The process of β-oxidation both reduces the amount of available labeled precursor and produces labeled small acids which could be (and often are) reincorporated into the metabolite. In order to increase the chances of observation of intact precursor

incorporation, two strategies have been adopted. Firstly, oxidation inhibitors have been developed and secondly, the concept of bond labeling has been employed. The two ^{13}C-labels in the hexaketide **50a** are at either end of the acyclic chain. After cyclization, the two labeled carbons in the decalin system are adjacent. If β-oxidation occurs, it is extremely unlikely that the labels could recombine in the final product such that correct bond labeling would be observed. The use of this labeling pattern allows verification of the intact incorporation of the labeled precursor since a ^{13}C-^{13}C coupling will be observed in the ^{13}C NMR spectrum of the isolated metabolite.

The β-oxidation process can be retarded by the use of inhibitors, as seen from the intact incorporation of the di- and tetraketides into dehydrocurvularin (**143**).[11] The successful β-oxidation inhibitors used in the dehydrocurvularin (**143**) experiments increase the amount of intact incorporation of the diketide and tetraketide precursors (**144** and **145**, respectively) (Figure 33). Co-injection of the tetraketide precursor **145** with ethyl 3-hydroxy-4-pentynoate **146** and 3-tetradecylthiopropanoic acid **147** led to an increase in the amount of intact incorporation from 7% to 16% and 70%, respectively.

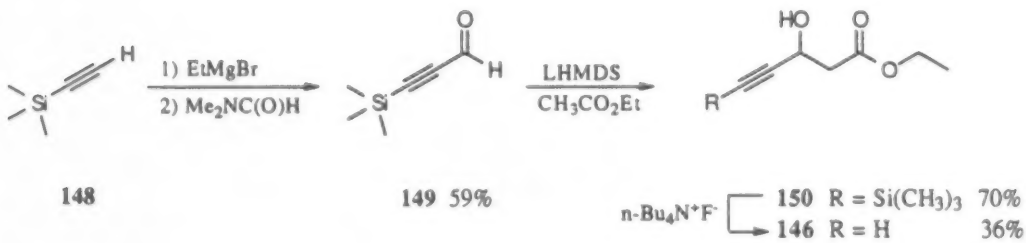
Figure 33. β-Oxidation inhibitors used for intact incorporation of diketide **144** and tetraketide **145** into dehydrocurvularin (**143**)



The former inhibitor **146** also allowed for 14% intact utilization of the diketide **144**. Ethyl 3-hydroxy-4-pentynoate **146** is thought to mimic the L-3-hydroxyacyl-CoA ester. Oxidation by L-3-hydroxyacyl-CoA dehydrogenase could lead to 3-oxo-4-pentynoate, a highly reactive Michael acceptor which may inactivate the enzyme by alkylation.[11b] 3-Tetradecylthiopropanoic acid **147** inhibits acyl-CoA dehydrogenase.[140]

The recent success of the β-oxidative inhibitors[11] encouraged their use in the present study. Ethyl 3-hydroxy-4-pentynoate **146** was synthesized using the literature protocol.[11a] Thus, the intermediate obtained from the treatment of (trimethylsilyl)acetylene **148** with ethyl magnesium bromide, is quenched with DMF to deliver the acetylene aldehyde **149** (Scheme 52). Condensation between the enolate of ethyl acetate and the aldehyde **149** affords the silyl-protected product **150**, which is then deprotected to furnish the desired inhibitor **146**. The acetylene **146** and the 3-tetradecylthiopropanoic acid **147** are potential β-oxidation inhibitors, but in our study, the hexaketide is also suspectible to a second oxidative degradative process, ω-oxidation.

Scheme 52.



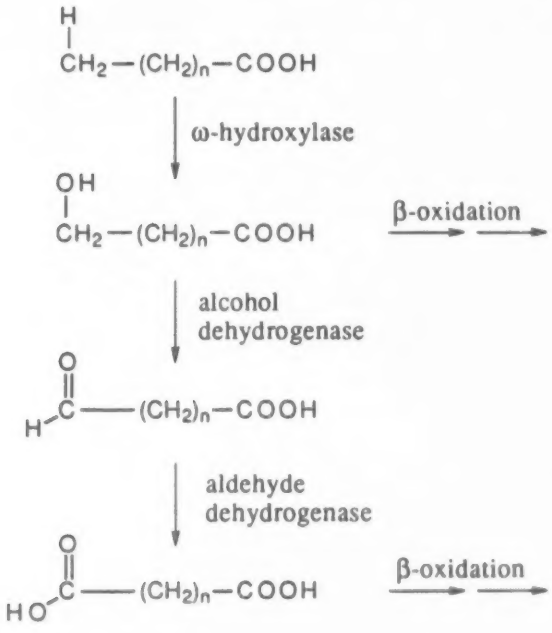
148 **149** 59%

ω-Oxidation of Fatty Acids

Medium to long chain fatty acids (C_{10}-C_{18}) can be degraded by ω-oxidation, a process involving three oxidative steps to give dicarboxylic acids. The free fatty acids are initially hydroxylated at the alkyl terminus by microsomal ω-hydroxylases to

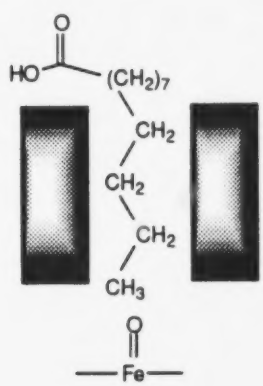
ω-hydroxymonocarboxylic acids,[141] with the medium-chain lengths being most easily hydroxylated (Scheme 53).[142] The rat liver ω-hydroxylation system contains two, or possibly three, cytochrome P-450 enzymes, which function in ω- and (ω-1)-hydroxylations.[143] The ω-hydroxylated products can then be β-oxidized in both the mitochondria and in the peroxisomes, or ω-oxidized further, first by microsomal or cytosolic alcohol dehydrogenases and then by the aldehyde dehydrogenase in the cytosol to generate dicarboxylic acids.[144,141c,145] Dicarboxylic acids are further metabolized by β-oxidation, believed to take place mainly in the peroxisomes,[146] to C_6-C_{10} dicarboxylic acids.[147] Although this sequence of events is not the major metabolic pathway of fatty acids,[148] it has been found to be increased by the presence of β-oxidation inhibitors[149] or changes in physiological conditions (e.g. diabetes).[150]

Scheme 53.



The fatty acid ω-hydroxylation steps are particularly interesting from a mechanistic point of view since the oxidation of the terminal methyl group is thermodynamically disfavored. The bond dissociation energies[151] for the removal of a hydrogen atom to give the methyl, isopropyl, and *tert*-butyl radicals are 98.0, 94.5, and 91.0 kcal mol^{-1}, respectively. Hence the bond strengths decrease in the order primary > secondary > tertiary. Hydroxylations must override the inherent specificity of the catalytic species for the weaker C-H bond. It has been suggested that the active site of lauric acid ω-hydroxylases must be highly structured in the vicinity of the activated oxygen to suppress the ω-1-hydroxylation (Figure 34).[152] The active site exerts reaction control by allowing only the terminal methyl group to reach the activated oxygen, as suggested by experiments using model metalloporphyrin systems.[153] The access to oxygen is probably governed by steric constraints within the catalytic site, since the enzyme can tolerate fatty acids of different lengths which implies that the terminal methyl specificity is not controlled by a specific interaction of the carboxyl group and the protein.[152]

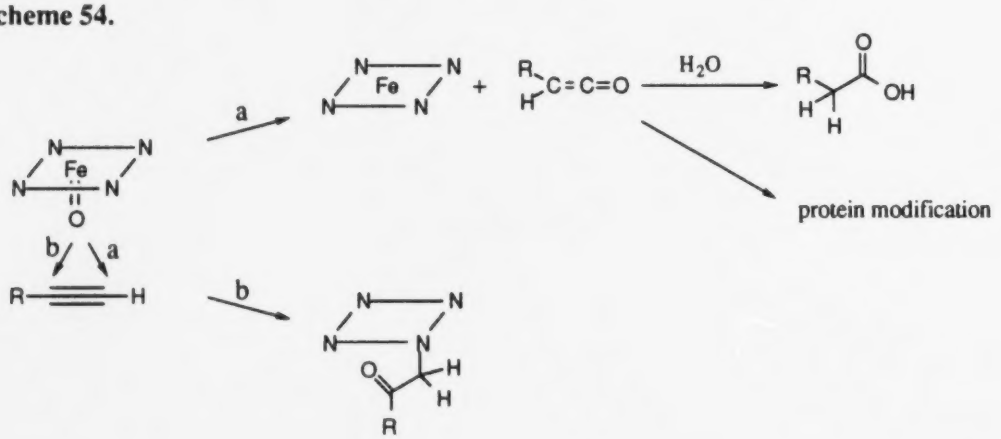
Figure 34. Proposed active site for ω-hydroxylation



Inhibition of ω-Oxidation

Study of the physiological role of the ω-oxidation reaction has been aided by the use of mechanism-based inactivators, also known as "suicide substrates."[154] Ortiz de Montellano and Reich have synthesized terminal acetylene fatty acids that are highly selective inhibitors of rat liver P-450 enzymes, without affecting the total P-450 levels or the other P-450 dependent activities.[143] The inactivation of cytochrome P-450 enzymes by the acetylenic inhibitors may proceed by either *N*-alkylation of the prosthetic heme group or by protein acylation (Scheme 54). *N*-Alkylation (path b) of the heme produces a green pigment and loss of the P-450 chromophore[155] by the addition of the oxygen to the internal carbon and porphyrin nitrogen addition to the terminal carbon of the triple bond.[152] Protein acylation (path a) may result from the *in situ* generation of a reactive ketene species. The oxygen could be transferred to the terminal carbon with concomitant migration of the terminal hydrogen to the vicinal carbon. The ketene can react with water to yield diacids (isolable) or acylate the protein causing inactivation.[152]

Scheme 54.

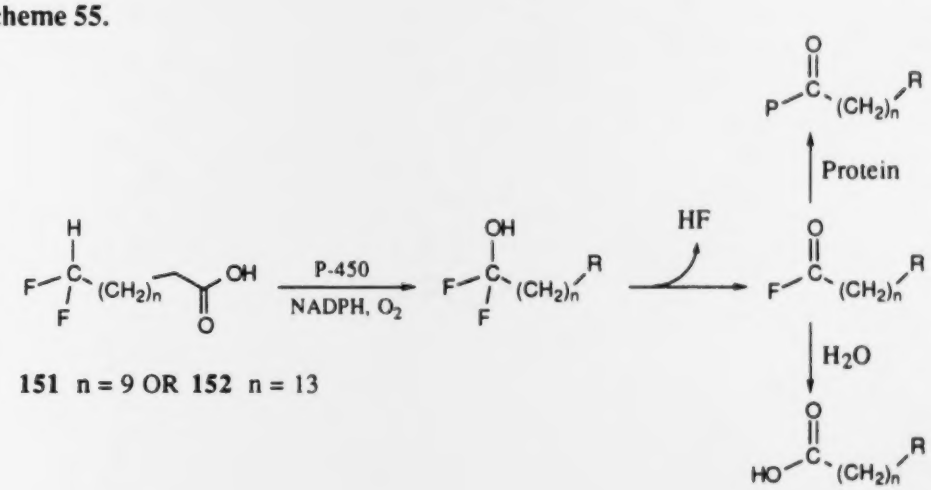


The hexaketide **50a**, which may be an intermediate in lovastatin biosynthesis, resembles the C_{12} carbon-chain of lauric acid, which is known to undergo ω-oxidation in the presence of β-oxidation inhibitors.[149] Although β-oxidation inhibitors have been

successful in allowing intact incorporation of di- and tetraketides, their presence could trigger the ω-oxidative enzymes. In such a case, the combined use of β- and ω-oxidation inhibitors during the fermentation of *Apergillus terreus* would suppress the oxidative degradation of the labeled precursor allowing it to enter the polyketide synthase intact.

The stategy to inactivate the ω-hydroxylation centers on design of a mechanism-based inhibitor originating from lauric and palmitic acid derivatives. For example, an ω-difluoro analogue of the acids, **151** and **152**, could be transformed into an acyl fluoride which would act as an electrophile to cause protein modifications (Scheme 55). The use of acyl halides, generated *in situ*, as irreversible inactivators of enzymes has been reported.[156] The acyl chloride formed by chloramphenicol inactivates cytochrome P-450.[156a] In the fatty acid case, the unstable difluoro-alcohol[157] produced should subsequently lose hydrogen fluoride to give the acyl fluoride for reaction with a nucleophile present in the enzyme active site. The inactivation of the enzyme should allow the labeled precursor to be utilized without degradation.

Scheme 55.

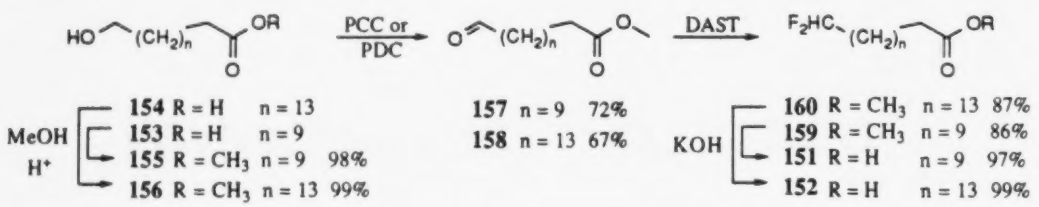


151 n = 9 OR **152** n = 13

The difluoro compounds synthesized are derivatives of lauric and palmitic acid. Esterification of the ω-hydroxyalkanoic acids **153** and **154** affords the methyl esters **155** and **156**, respectively,[158] which are then oxidized to the corresponding aldehydes **157** and

158 (Scheme 56). Diethylaminosulphur trifluoride (DAST)[159] converts the two aldehydes **157** and **158** to the respective ω-difluoro-products **159** and **160**; subsequent ester hydrolysis[104] produces the difluoro derivatives of lauric **151** and palmitic **152** acid.

Scheme 56.


HO (CH2)n OR
O
PCC or PDC
O (CH2)n O
O
DAST
F2HC (CH2)n OR
O
MeOH H+
154 R = H n = 13
153 R = H n = 9
155 R = CH3 n = 9 98%
156 R = CH3 n = 13 99%
157 n = 9 72%
158 n = 13 67%
KOH
160 R = CH3 n = 13 87%
159 R = CH3 n = 9 86%
151 R = H n = 9 97%
152 R = H n = 13 99%

Survival of Labeled Precursor and Incorporation Attempts

The tendency of the doubly-labeled NAC triene thioester **50a** to cyclize initially appeared to be an obstacle before it was shown that the stereochemistry of the products is different from that leading to lovastatin (**5**). A time study was done to determine the rate of cyclization of unlabeled NAC ester **50** (Scheme 57) in fermentation media at 28 °C without the addition of *Aspergillus terreus*. The percentage of triene **50** was determined by ^{1}H NMR data after its daily isolation from different fermentations. The results indicate that **50** has a half-life of approximately 24 h in both the growth, and production media, as well as a combination of both media (Figure 35). To determine whether the rate of cyclization could be enhanced by increased acidity, NMR samples of **50** in deuterated water and acetonitrile (two drops of methanol-d_6 were added to aid solubility) were adjusted to pH 5 and 7 and stored at 28 °C.

Scheme 57.

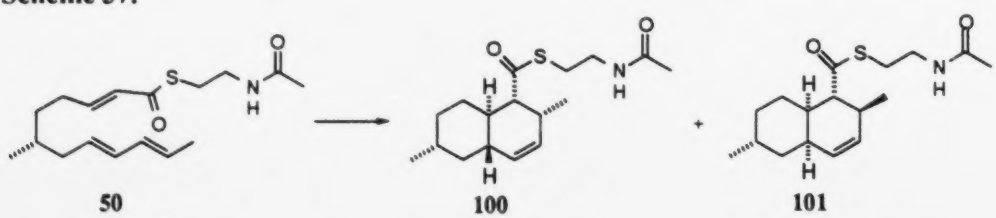
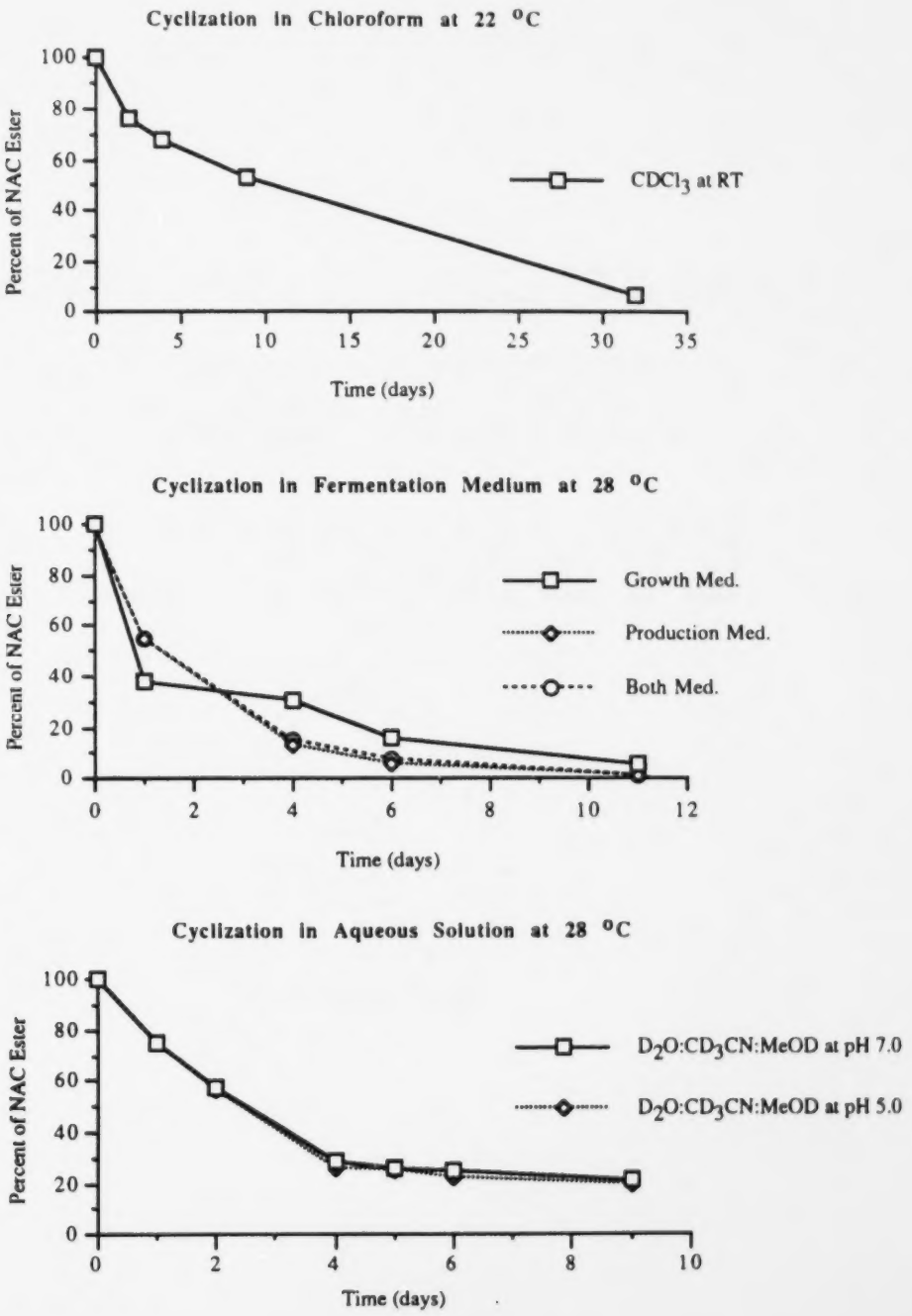


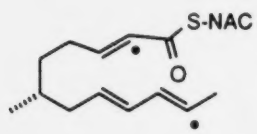
Figure 35. Rate of cyclization of the NAC ester **50** in various solutions



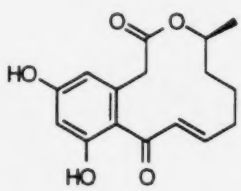
The rate of cyclization is almost identical for the two solutions and is similar to the rate found with the fermentation media (Figure 35). When the NAC ester **50** is left in chloroform at room temperature the half-life increases to about 10 days. The slower rate of cyclization in chloroform than in aqueous solutions may be attributed to differences in the solvent. Bimolecular Diels-Alder reactions with electron-deficient dienophiles are well-known to be accelerated in water.[160]

The key features for the successful incorporation of the advanced precursors into dehydrocurvularin (**143**) (Figure 36) are: 1) the timing of the precursor addition; 2) the presence of β-oxidative inhibitors; and 3) the use of high glucose replacement media.[11] It is known that high glucose concentrations can partially suppress the β-oxidation pathway in mammalian systems since their acetate requirements can be met by catabolism of the carbohydrates.[139]

Figure 36. Structures of triene NAC thioester **50a** and dehydrocurvularin (**143**)



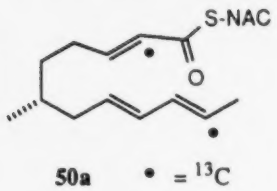
50a • = ^{13}C



143

The incorporation studies with the hexaketide **50a** have followed the above protocols. In a typical experiment, the labeled material is added by pulse feeding every 24 h over a three day period commencing on the third day of production fermentation. The β- and/or ω-oxidative inhibitors, if used, are added simultaneously with the precursor. The experiments include the use of replacement and new production media as well as addition of DMSO to the medium to aid transport of the precursor across the cell membrane (Figure 37).[161]

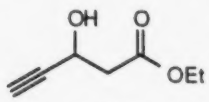
Figure 37. Incorporation experiments for conversion of triene **50a** to lovastatin (**5**)



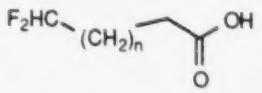
50a • = ^{13}C

$Me(CH_2)_{13}S(CH_2)_2COOH$

147



146



151 n = 9 and **152** n = 13

Precursor[a] **50a** (mg)[b]	**146** (mg)[b]	**147** (mg)[b]	**151** (mg)[b]	**152** (mg)[b]	Special Conditions
20					
20	75				
20		35			
20	75	35			
20	75				new production medium[c]
20		35			new production medium[c]
20	75	35			new production medium[c]
20	75				replacement medium
20		35			replacement medium
20		35			replacement medium
20	75				
20	75	35	50		
20	75	35		50	
20[d]	75[d]	35[d]	50[d]		extra 5 mL DMSO added[e]

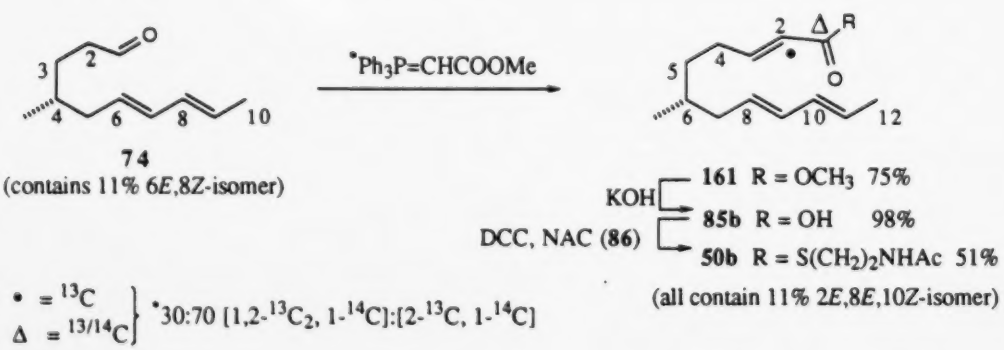
[a]Precursor and inhibitors added simultaneously to 2 x 500 mL flasks containing 125 mL medium each. [b]Total amount added after three pulse feedings (three equal portions in 0.35 mL 95% EtOH). [c]Medium contained no yeast extract or soy protein powder, but had $NaNO_3$ (3.0 g), $MgSO_4 \cdot H_2O$ (0.25 g), K_2HPO_4 (1.0 g), and $FeSO_4 \cdot 7H_2O$ (10 mg) added. [d]Material dissolved in 1 mL DMSO. [e]DMSO added in equal portions during the pulse feedings.

The new production medium does not contain soy protein powder or yeast extract, which are believed to enhance the cyclization of the hexaketide **50a**. The conditions summarized in Figure 37 produced no detectable ^{13}C-^{13}C coupling in the ^{13}C NMR spectrum of the lovastatin (**5**) isolated from these experiments.

The absence of any detectable ^{13}C-^{13}C coupling in the ^{13}C NMR spectrum, and the observation that the amount of reisolated labeled precursor **50a** averaged less than 1%, raises questions about the fate of **50a**. Presumably the triene is degraded before it has the opportunity to bind to the polyketide synthase. If the material enters the cell before it is broken down, it is possible that ^{13}C-labeled degradation products could be incorporated into lovastatin (**5**). However, this enrichment could not be detected *via* ^{13}C NMR or MS analysis. In order to increase the sensitivity of the experiment, the NAC ester was synthesized in a ^{14}C-labeled form.

To obtain the ^{14}C-labeled NAC thioester, the initial diene aldehyde **74** is reacted with a 30:70 mixture of [1,2-$^{13}C_2$, 1-^{14}C]:[2-^{13}C, 1-^{14}C]-Wittig reagents (isotopic purity 99% ^{13}C; 40 μCi) to deliver a mixture of triene methyl esters (Scheme 58). The major partially-purified 2*E*,8*E*,10*E*-isomer **161,** still contaminated with the 2*E*,8*E*,10*Z*-isomer (11% by ^1H NMR integration), is hydrolyzed to the free acid **85b**, followed by coupling with *N*-acetylcysteamine (**86**) to afford **50b** (22.3 μCi/mmol).

Scheme 58.



The material **50b** has recently been incorporated by pulse feedings into fermentations of *Aspergillus terreus* MF 4845 by Dr. Yuko Yoshizawa. The initial results demonstrate that the major portion of the radioactivity resides in the mycelium (68%) with the aqueous broth containing 24%, and the remaining 8% lost through an unknown mechanism (metabolism to CO_2?). The lovastatin isolated from the mycelium extracts was not ^{14}C-labeled, and there was no detectable NAC-ester or free acid triene as indicated by TLC. This indicates that the radioactivity is bound to or contained within the cell membrane. The exact locations of the radioactivity in the degraded or transformed hexaketide material **50b** remain to be determined.

The success of an incorporation study sometimes requires the tailoring of conditions to allow utilization of the advanced precursor, and it is not uncommon to undertake many experiments before optimization can be achieved. In our laboratory, Dr. Yuko Yoshizawa is currently investigating the use of protoplasts,[162] saponin,[163] and 2,6-*O*-dimethyl-β-cyclodextrin[164] to assist the incorporation of advanced precursors. The first two methods rely on increasing the permeability of the fungal cell membrane to ease the precursor's transport into the cell. The cyclodextrin derivative is believed to stimulate the uptake of precursors, although a possible mechanism for this has not been suggested.[164] Mr. Yaoquan Liu is examining an active transport stategy to enhance the already successful incorporations of di- and tetraketides into dehydrocurvularin (**143**) from *Alternaria cinerariae* . The acetyl end of the *N*-acetylcysteamine will be functionalized to allow an easily dissociable linkage to be formed between the precursor and a carrier. The carrier, which may be a peptide or carbohydrate, could allow for transport of the precursor across the cell membrane. Once within the cell, the linkage could be cleaved by a hydrolytic enzyme leaving the advanced intermediate available for incorporation. The above tactic, if successful for dehydrocurvularin (**143**), could also be easily applied to the hexaketide **50a**. Finally, molecular biological techniques would allow generation of cell free polyketide synthase systems which could accept precursor

like the hexaketide **50a**. Presently, cell free systems are allowing incorporation of labeled acetates into novel polyketide metabolites.[23]

In summary, the synthesis of labeled hexaketide NAC thioester **50a** can be achieved in 13 steps from commercially available (*R*)-citronellol with an overall yield of 4.0%. The non-enzymatic Diels-Alder reactions of unlabeled triene NAC thioester **50**, its ethyl ester **83**, and its free acid **85** yield the two analogous diastereomers in each case, under either thermal or Lewis acid conditions. The synthesis of reference compound **93** aided the structure elucidation of the two generated cycloadducts, *trans*-fused **92** and *cis*-fused **94**. The *trans*-fused reference material **93**, containing the same stereochemistry in the bicyclic ring as 4a,5-dihydromonacolin L (**8**), was generated from L-glutamic acid in 13 steps in 0.7% overall yield. Since **93** was not detected in the *in vitro* cyclizations, the incorporation of labeled hexaketide **50a** into lovastatin (**5**), after inoculation and fermentation, would lend support to the existence of a cyclase enzyme.

EXPERIMENTAL

General

All non-aqueous reactions requiring anhydrous conditions were performed under a positive pressure of argon (Ar) in oven- or flame-dried glassware, which had been cooled under Ar . All solvents for anhydrous reactions were dried according to Perrin *et al.*[165] THF, diethyl ether, benzene, toluene, mesitylene, and cymene were distilled from sodium and benzophenone. Triethylamine, *N*,*N*-diisopropylethylamine, pyridine, DMF, chloroform, dichloromethane, carbon tetrachloride, and HMDS were distilled from calcium hydride. Anhydrous ethanol and methanol were purified by distillation from magnesium metal and catalytic iodine. The removal of solvents refers to evaporation *in vacuo* on a rotary evaporator followed by evacuation to constant sample weight (<0.1 mm Hg). Solvents used for chromatography were distilled. Water used was Milli-Q (Millipore Corp.; Milford, MA) quality.

All reagents employed were of American Chemical Society (ACS) grade or finer. All commercially available labeled compounds were purchased from Cambridge Isotope Laboratories (Woburn, MA). Commercial organometallic reagents were obtained from Aldrich Chemical Co. *n*-Butyllithium solution was periodically titrated against menthol / phenanthroline. LHMDS was titrated against menthol / fluorene before use. Air sensitive reagents were handled under an atmosphere of dry Ar. Freeze-dried specimens of *Aspergillus terreus* MF4845 were a generous gift from Merck Research Laboratories (Rahway, NJ). Mosher's reagent, (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride, was prepared according to the procedure of Dale.[82]

Where possible all reactions were followed by thin layer chromatography (TLC) and visualized using UV fluorescence, iodine staining, and/or dodecamolybdophosphoric acid. Commercial thin layer and preparative layer chromatography plates were: normal silica (Merck 60 F-254) or reverse-phase (Merck RP-8 or RP-18 F-254S). Silica gel for column chromatography was Merck type 60, 70-230 mesh or its equivalent from General

Intermediates of Canada (Edmonton, AB). Flash chromatography was performed according to Still *et al.* using Merck type 60, 230-420 mesh silica gel.[166] Normal phase medium pressure liquid chromatography (MPLC) used a column of Merck Kieselgel 60 H (*ca.* 55 g, 2.5 x 30 cm). Reverse phase MPLC was performed on a Merck Lobar Lichroprep RP-8 column, size B. Silver-stained thin layer chromatography plates (Merck 60 F-254) were prepared by quick immersion in 10% aqueous $AgNO_3$, followed by reactivation by heating to 60 °C at 20 mm Hg for 12 h in the dark. Silver-stained silica gel (Merck type 60, 70-230 mesh) for MPLC column (30 x 4 cm) chromatography was prepared by immersion in 15% $AgNO_3$ (1:1 ethanol:acetonitrile) and after solvent removal, the silica gel was dried in a similar manner as the TLC plates. All solvent mixtures are listed as volume ratios, and all medium pressure liquid chromatography was performed using solvents which were previously degassed under vacuum.

High pressure liquid chromatography (HPLC) was performed on a Beckman System Gold instrument equipped with a model 166 variable wavelength UV detector set at 254 nm (for citronellol derivatives and lovastatin), and an Altex 210A injector with a 100 μL sample loop. The columns were Waters Nova-Pak cartridges (reverse phase 8NVC18 4 μ C_{18} column, 1 x 10 cm) encased in a Waters Z-module compression unit. HPLC grade acetonitrile (190 nm cutoff) and methanol were obtained from Terochem (Edmonton, AB). All HPLC solvents were prepared fresh daily and filtered with a Millipore filtration system under vacuum before use.

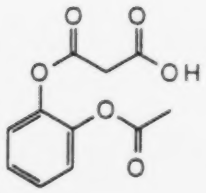
The determination of the enantiomeric excess of (*R*)-citronellol was performed on a Varian Vista 6000 gas chromatograph with a split injector (200 °C; 1:50) and a J & W DB-5 fused-silica capillary column (30m x 0.25 I.D.; film thickness 0.25 μm) connected to a VG7070E mass spectrometer with detection *via* total ion current. The column temperature was programmed from 100 to 260 °C at 4 °C/min.

All literature compounds had IR, ^1H NMR, and mass spectra consistent with the assigned structures. Melting points are uncorrected and were determined on a Thomas

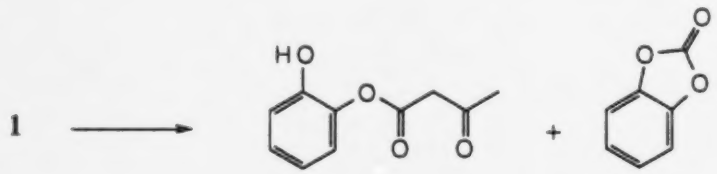
Hoover or Büchi oil immersion apparatus using open capillary tubes. Temperatures for Kugelrohr distillation were those of the air bath surrounding the distillation flask, and did not necessarily represent true boiling points (bp). Optical rotations were measured on Perkin Elmer 241 or 141 polarimeters with a microcell (100 mm, 1 mL) at ambient temperature. All specific rotations reported were measured at the sodium D line and values quoted are valid within ±1 °. Infrared spectra (IR) were recorded on a Nicolet 7199 or 20SX FT-IR spectrometer. Mass spectra (MS) were recorded on a Kratos AEI MS-50 (high resolution, electron impact ionization), MS-12 (chemical ionization, CI, NH_3), and MS-9 (fast atom bombardment with argon, posFAB) instruments. Cleland matrix in posFAB spectra refers to a 5:1 mixture of dithiothreitol and dithioerythritol. Microanalyses were obtained using a Perkin Elmer 240 or Carlo Erba 1108 CHN analyzer.

Nuclear magnetic resonance (NMR) spectra were measured on Bruker WH-200, AM-300, WM-360, WH-400, or Varian 500 instruments in the specified solvent with tetramethylsilane (TMS) as internal standard for ^{1}H NMR. For ^{13}C NMR spectra, the deuterated solvent peak was used as the reference with its position set relative to TMS. For ^{19}F NMR spectra, $CFCl_3$ was added and used as the internal reference.

Radioactivity was determined using standard liquid scintillation procedures in plastic 10 mL scintillation vials (Terochem) with Beckman Ready Gel scintillation cocktail (Fullerton, CA). The instrument used was a Beckman LS 5000TC with automatic quench control to directly determine decompositions per minute (dpm) in the labeled samples by comparison against a quench curve prepared from Beckman ^{3}H and ^{14}C quenched standards. Radioactive TLC plates were analyzed with a Berthold LB2760 TLC-scanner.

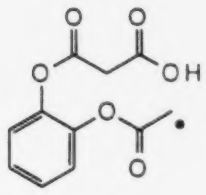


Catechol Acetate Malonate (1).[66] The same method as for the preparation of malonate derivative **16** was employed. Thus, acylation of catechol monoacetate (**19**) (0.616 g, 4.05 mmol) with malonic acid monochloride (**15**) (0.815 g, 6.65 mmol) afforded a brown oil, which was purified by flash chromatography (SiO_2; 50% EtOAc in hexane + 1% formic acid, *Rf* 0.20) to give a yellow solid. Recrystallization from toluene yielded white crystals of **1** (609 mg, 63%): mp 103-104 °C (lit.[66] mp 103-104 °C); IR ($CHCl_3$ cast) 3600-2400 (br m), 1771 (s), 1749 (m), 1494 (s), 1244 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 11.8–10.9 (br s, 1H, COO<u>H</u>), 7.34-7.13 (m, 4H, Ar-<u>H</u>), 3.63 (s, 2H, C<u>H</u>$_2$), 2.30 (s, 2H, C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.29 (<u>C</u>OOH), 168.77 (<u>C</u>(O)CH_3), 163.58 (<u>C</u>(O)OAr), 141.98 (*ipso*-C), 141.71 (*ipso*-C), 127.22 (<u>C</u>H), 126.76 (<u>C</u>H), 123.68 (<u>C</u>H), 123.15 (<u>C</u>H), 40.85 (<u>C</u>H_2), 20.58 (<u>C</u>H_3); MS (CI, NH_3) 256 (MNH_4^+, 100); Anal. Calcd for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23. Found: C, 55.21; H, 4.40.



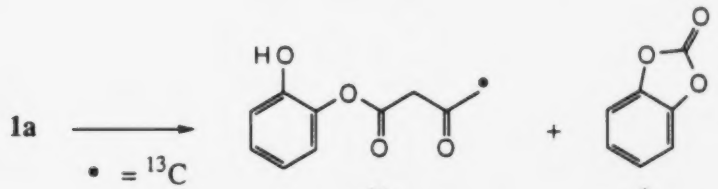
2 **3**

Condensation Reaction Using Catechol Acetate Malonate (1).[66] The same method as for the condensation of malonate derivative **16** was adopted. Thus, treatment of **1** (131 mg, 0.552 mmol) with *i*-PrMgBr (0.22 M, 1.10 mmol) afforded a yellow liquid, which consisted of 30% catechol carbonate (**3**) and 10% catechol monoacetoacetate (**2**) by comparison of the physical and spectral properties of **3** (see condensation reaction using **1a** below) and **2**, respectively.



• = ^{13}C

Catechol [2-^{13}C]-Acetate Malonate (1a). The same method as for the preparation of **16** was employed. Thus, treatment of catechol [2-^{13}C]-monoacetate (**19a**) (1.28 g, 8.36 mmol) with malonic acid monochloride (**15**) (2.05 g, 16.7 mmol) afforded **1a** (1.66 g, 83%) as a white solid: mp 103-104 °C (lit.[66] mp for unlabeled compound 103-104 °C); IR (KBr) 3600-2400 (br m), 1765 (s), 1704 (s), 1492 (m), 1243 (m), 1209 (s), 1156 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.8–10.9 (br s, 1H, COO<u>H</u>), 7.36-7.15 (m, 4H, Ar-<u>H</u>), 3.63 (s, 2H, C<u>H</u>$_2$), 2.29 (d, 2H, J = 130.1 Hz, ^{13}C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.32 (<u>C</u>OOH), 168.93 (d, J = 60.9 Hz, <u>C</u>(O)^{13}CH$_3$), 164.05 (<u>C</u>(O)OAr), 141.95 (*ipso*-C), 141.75 (*ipso*-C), 127.15 (<u>C</u>H), 126.75 (<u>C</u>H), 123.62 (<u>C</u>H), 123.16 (<u>C</u>H), 40.93 (<u>C</u>H$_2$), 20.55 (^{13}<u>C</u>H$_3$); MS (CI, NH_3) 257 (MNH_4^+, 65), 256 (100), 240 (8), 239 (66).

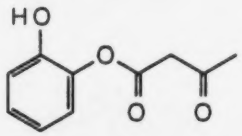


1a → (• = ^{13}C) **2b** + **3**

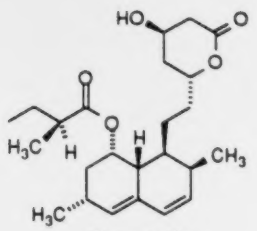
Condensation Reaction Using Catechol [2-^{13}C]-Acetate Malonate (1a). The same method as for the condensation of malonate derivative **16** was followed. Thus, treatment of **1a** (0.250 g, 1.05 mmol) with *i*-PrMgBr (0.67 M, 2.19 mmol) afforded two products: catechol [4-^{13}C$_1$]-monoacetoacetate (**2b**) (42.1 mg, 21%, Rf 0.21); and catechol carbonate (**3**) (61.5 mg, 30%).

Data for catechol [4-$^{13}C_1$]-monoacetoacetate (**2b**): IR ($CHCl_3$ cast) 3600-3000 (br s), 1767 (br s), 1711 (br s), 1607 (m), 1599 (m), 1495 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.23-6.83 (m, 4H, Ar-H), 3.81 (s, 2H, CH_2), 2.37 (d, 3H, J = 128.9 Hz, $^{13}CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.29 (d, J = 42.5 Hz, C(O)$^{13}CH_3$), 165.27 (C(O)O), 147.81 (*ipso*-C), 137.55 (*ipso*-C), 127.62 (CH), 122.48 (CH), 120.07 (CH), 117.31 (CH), 49.90 (d, J = 14.5 Hz, CH_2), 30.16 ($^{13}CH_3$); MS (EI) calcd for $^{13}C^{12}C_9H_{10}O_4$ 195.0613, found 195.0626 (M^+, 6), 110.0326 (100).

Data for catechol carbonate (**3**): mp 115-117 °C (lit.[66] 116-118 °C); IR ($CHCl_3$ cast) 1835 (m), 1725 (m), 1240 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.27 (br s, 4H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.35 (C(O)O), 143.25 (*ipso*-C), 124.92 (CH), 110.50 (CH); MS (EI) calcd for $C_7H_4O_4$ 136.0160 found 136.0166 (M^+, 23), 110.0366 (100).



Catechol Monoacetoacetate (2).[66] A modification of the procedure of Yoo was used.[66] Diketene (0.714 mL, 9.26 mmol) was slowly added to a solution of catechol (1.02 g, 9.26 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 6 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 40% EtOAc in hexane, Rf 0.27) to give **2** (418 mg, 23%) as a thick oil: IR ($CHCl_3$ cast) 3600-3050 (br m), 1768 (br s), 1712 (br s), 1611 (m), 1602 (m), 1499 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.23-6.83 (m, 4H, Ar-H), 3.81 (s, 2H, CH_2), 2.37 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.12 (C(O)), 165.35 (C(O)O), 147.57 (*ipso*-C), 137.37 (*ipso*-C), 127.41 (CH), 122.43 (CH), 119.96 (CH), 116.96 (CH), 49.46 (CH_2), 29.69 (CH_3); MS (EI) calcd for $C_{10}H_{10}O_4$ 194.0579, found 194.0578 (M^+, 1.2), 110.0369 (100).

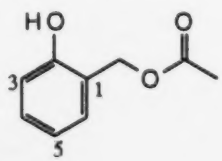


Lovastatin
5

General Procedure for Fermentation of *Aspergillus terreus*, and Isolation of Lovastatin (5). One freeze-dried specimen of *Aspergillus terreus* MF 4845 (originally obtained as a gift from Merck Research Laboratories, Rahway, NJ) was soaked in H_2O (1 mL) for 5 min, and the resulting spore suspension was added to 10 slants (2-3 drops per slant), prepared from bacto malt agar (Difco Laboratories; Detroit, MI) (7.2 g), potato dextrose broth (Difco) (6.0 g), and H_2O (300 mL) which had been sterilized at 121 °C for 20 min. The inoculated slants were incubated at 25-28 °C for 12 days and then stored at 4 °C until needed. The resulting mycelium from one slant was suspended in H_2O (2 mL), and the suspension was added to an Erlenmeyer flask (500 mL), containing the growth medium prepared from: glucose (1.0 g), oat flour (1.0 g), tomato paste (4.0 g), corn steep solids (0.25 g) and trace element solution (1 mL) dissolved in MilliQ water to 100 mL. The mixture was autoclaved at 121 °C for 20 min before inoculation. The trace element solution consisted of: $FeSO_4 \cdot 7H_2O$ (1.0 g), $MnSO_4 \cdot 4H_2O$ (1.0 g), $CuCl_2 \cdot 2H_2O$ (25.0 mg), $CaCl_2 \cdot 2H_2O$ (0.10 g), H_3BO_3 (56.0 mg), $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (19.0 mg), $ZnSO_4 \cdot 7H_2O$ (0.20 g) dissolved in MilliQ water to 1 L. The growth medium was incubated in a fermenter at 28 °C and 220 rpm in the dark for 24 h. Portions (10 mL) of the resulting suspension were then transferred to each of 8 flasks containing the production medium (125 mL/flask) prepared from the following: lactose (60.0 g), ardamine pH (Champlain Inc.; Clifton, NJ) (10.0 g), soy protein powder (2.0 g), betaine (0.60 g), KCl (2.0 g), and polyethylene glycol 2000 (1.0 g) dissolved in MilliQ water to 1 L. The flasks were then incubated under the same conditions as above for an additional 7-9 days.

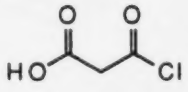
The combined fermentation mixtures were acidified to pH 3.0 by 1N HCl, homogenized with ethyl acetate (300 mL) in a Waring blender (2 x 30 s) and filtered. The solid material was homogenized with an additional 100 mL of EtOAc and filtered. The combined aqueous layers were extracted with EtOAc (2 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, leaving a black viscous oil. The oil in distilled toluene (50 mL) was heated to reflux for 2 h under Ar with continuous removal of H_2O (CaH_2 Soxhlet). After cooling, the toluene was evaporated *in vacuo*, and the residue was separated sequentially by: 1) flash chromotagraphy (SiO_2; 70% EtOAc in hexane, R_f 0.20); and 2) flash chromatography (SiO_2; 30% EtOAc in CH_2Cl_2, R_f 0.25). The resultant solid was recrystallized (EtOAc) to typically yield 120 mg of pure lovastatin. All physical and chromatographic properties were identical to those reported earlier.[46]

General Procedure for Fermentation of *Aspergillus terreus*, and Inoculation of the Hexaketide (50a). The fermentations of *Aspergillus terreus* employed the same conditions as described above except only two 500 mL Erlenmeyer flasks each containing 125 mL of production medium were used. The labeled precursor **50a** (20 mg) in 95% ethanol (1 mL) was added equally in 3 portions at 12 h intervals after 3 days of production (i.e. not including 24 h growth period). The β- or ω-oxidation inhibitors, if used, were added simultaneously with the precursor. After 8 days, the lovastatin (**5**) was isolated using the extraction and purification procedures previously described.

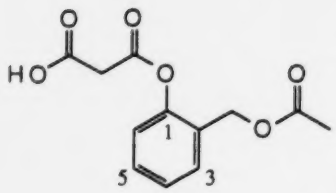


2-Hydroxybenzyl Acetate (14). Distilled acetyl chloride (1.15 mL, 16.2 mmol) was slowly added to a solution of 2-hydroxybenzyl alcohol (2.00 g, 16.1 mmol) and

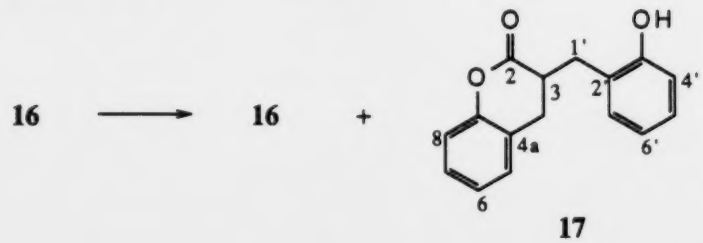
distilled *N,N*-dimethylaniline (2.23 mL, 17.6 mmol) in dry Et_2O (20 mL), and the reaction mixture was heated to reflux for 2 h. After cooling, the solution was diluted with Et_2O (200 mL) and washed with 2N HCl (2 x 150 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). Concentration *in vacuo* gave a pale orange liquid, which was purified by flash chromatography (SiO_2; 50% EtOAc in hexane, *Rf* 0.54) to afford **14** (2.25 g, 84%) as a clear oil: IR ($CHCl_3$ cast) 3600-3200 (br s), 1737 (s), 1708 (s), 1458 (s), 1279 (s), 1242 (s), 1181 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (br s, 1H, OH), 7.36-7.20 (m, 2H, Ar-H), 7.00-6.84 (m, 2H, Ar-H), 5.13 (s, 2H, $OC\underline{H}_2$), 2.10 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.46 ($\underline{C}(O)CH_3$), 155.37 (C-2), 131.93 ($\underline{C}H$), 130.94, ($\underline{C}H$) 121.68 (C-1), 120.50 ($\underline{C}H$), 117.50 ($\underline{C}H$), 63.13 ($O\underline{C}H_2$), 20.80 ($\underline{C}H_3$); MS (EI) calcd for $C_9H_{10}O_3$ 166.0630, found 166.0629 (M^+, 42), 106.0420 (100); Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.23; H, 6.00.



Malonic Acid Monochloride (15).[64] A solution of malonic acid (15.0 g, 144 mmol) and thionyl chloride (11.0 mL, 151 mmol) in dry Et_2O (53 mL) was heated to reflux for 5.5 h. After cooling, the solvent was removed *in vacuo* to leave a green solid. Distilled 1-chlorobutane was added to the solid and the mixture was stirred at 50 °C for 45 min. The hot solution was filtered to remove the green solid and the orange filtrate was allowed to cool. The resulting yellow crystals were collected to yield malonic acid monochloride (**15**) (4.47 g, 25%): mp 64-65 °C (dec) [lit.[64] mp 60-63 °C (dec)]; IR ($CHCl_3$ cast) 3700-2200 (br m), 1780-1580 (br s), 1437 (m), 1400 (m), 1229 (m), 1177 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 10.40–9.80 (br s, 1H, $COO\underline{H}$), 3.92 (s, 2H, $C\underline{H}_2$); Anal. Calcd for $C_3H_3ClO_3$: C, 29.41; H, 2.47. Found: C, 29.48; H, 2.44.



2-Acetyloxymethyl-1-phenyl Malonate (16). A modification of the procedure of Yoo was employed.[66] A solution of malonic acid monochloride (**15**) (1.45 g, 11.8 mmol) in dry THF (10 mL) at -78 °C was slowly added to a cooled (-78 °C) solution of **14** (1.15 g, 6.89 mmol) in dry THF (20 mL). The mixture was allowed to warm to room temperature, and then was heated at reflux for 2 h. After cooling, the mixture was concentrated *in vacuo* to give a brown oil. The residue was purified by flash chromatography (SiO_2; 25% EtOAc in hexane + 1% formic acid, R_f 0.30) to give **16** (1.36 g, 78%) as an oil: IR ($CHCl_3$ cast) 3600-2400 (br m), 1759 (br s), 1745 (br s), 1494 (m), 1455 (m), 1385 (s), 1246 (br s), 1230 (br s), 1174 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.10–9.60 (br s, 1H, COO<u>H</u>), 7.41 (dd, 1H, J = 7.4, 1.9 Hz, H-3), 7.34 (ddd, 1H, J = 7.9, 7.5, 1.9 Hz, H-5), 7.23 (ddd, 1H, J = 7.5, 7.4, 1.9 Hz, H-4), 7.12 (dd, 1H, J = 7.9, 1.9 Hz, H-6), 5.10 (s, 2H, OC<u>H</u>$_2$), 3.70 (s, 2H, C<u>H</u>$_2$), 2.10 (s, 2H, C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.36 (<u>C</u>(O)O), 170.44 (<u>C</u>(O)O), 164.71 (<u>C</u>(O)O), 148.74 (C-1), 130.61 (<u>C</u>H), 129.79 (<u>C</u>H), 127.69 (C-2), 126.63 (<u>C</u>H), 122.50 (<u>C</u>H), 61.54 (O<u>C</u>H$_2$), 41.11 (<u>C</u>H$_2$), 20.76 (<u>C</u>H$_3$); MS (CI, NH_3) 270 (MNH_4^+, 100), 253 (MH^+, 0.3); Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 56.85; H, 4.80.

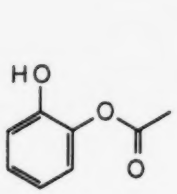


17

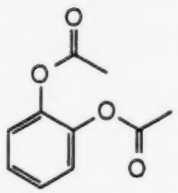
Condensation Reaction Using 2-Acetyloxymethyl-1-phenyl Malonate (16). A modification of the procedure of Yoo was adopted.[66] A solution of 2-malonylbenzyl

acetate (**16**) (0.210 g, 0.833 mmol) in dry THF (8 mL) was treated at -5 °C with isopropyl magnesium bromide (0.80 M, 1.67 mmol), which was freshly prepared from isopropyl bromide and magnesium turnings. The reaction mixture was allowed to warm to room temperature and was stirred for 44 h. The mixture was poured onto ice-cooled 1N HCl (5 mL) and rapidly extracted with Et_2O (2 x 25 mL). The combined Et_2O fractions were washed with H_2O (20 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resultant yellow residue was purified by flash chromatography (SiO_2; 40% EtOAc in hexane, *Rf* 0.57) to afford 3-(2-hydroxybenzyl)-dihydrocoumarin (**17**) (43.1 mg, 25%) as a white solid, and starting material **16** (56.0 mg, 32%, *Rf* 0.12).

Data for **17**: mp 140-141 °C; IR ($CHCl_3$ cast) 3600-3100 (br m), 1780-1680 (br m), 1458 (m), 1229 (m), 1135 (br m), 1050 (br s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (ddd, 1H, *J* = 8.1, 7.4, 1.6 Hz, H-7), 7.16 (br d, 1H, *J* = 7.5 Hz, H-5), 7.15 (ddd, 1H, *J* = 8.1, 7.7, 1.7 Hz, H-5'), 7.10 (dd, 1H, *J* = 7.4, 1.1 Hz, H-7'), 7.09 (ddd, 1H, *J* = 7.5, 7.4, 1.1 Hz, H-6), 7.04 (br d, 1H, *J* = 8.1 Hz, H-8), 6.88 (ddd, 1H, *J* = 8.1, 7.4, 1.2 Hz, H-6'), 6.87 (br d, 1H, *J* = 7.7 Hz, H-4'), 6.52 (br s, 1H, OH), 3.26 (dd, 1H, *J* = 14.0, 5.8 Hz, 1 x H-1'), 3.09 (dddd, 1H, *J* = 12.2, 6.6, 5.9, 5.8 Hz, H-3), 2.99 (dd, 1H, *J* = 14.0, 5.9 Hz, 1 x H-1'), 2.95-2.89 (m, 2H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.92 (C-2), 154.33 (C-3'), 151.33 (C-8a), 131.60 (C-7'), 128.42 (CH), 128.28 (CH), 128.10 (CH), 124.57 (C-6), 124.28 (C-2'), 122.82 (C-4a), 120.64 (C-6'), 116.82 (C-4'), 116.57 (C-8), 40.00 (C-3), 30.18 (C-1'), 28.97 (C-4); MS (EI) calcd for $C_{16}H_{14}O_3$ 254.0943, found 254.0941 (M^+, 100), 160.0522 (30), 147.0446 (66).



19



20

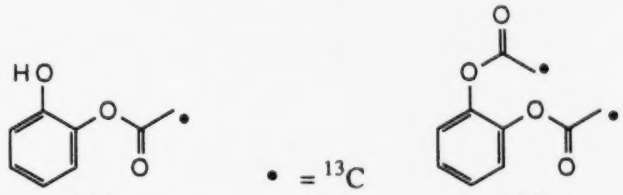
Catechol Monoacetate (19).[66,67] **Procedure A.** Distilled acetyl chloride (0.67 mL, 9.46 mmol) was slowly added to a solution of catechol (0.992 g, 9.01 mmol) and distilled *N,N*-dimethylaniline (1.26 mL, 9.94 mmol) in dry Et_2O (10 mL). The mixture was heated to reflux for 2 h, and the solvent was removed *in vacuo* to furnish a 1:1:1 mixture of catechol : monoacetate : diacetate (1.01 g, 74%). The resultant oil was redissolved in toluene (75 mL), and washed with H_2O (100 mL). The aqueous layer was extracted with toluene (2 x 50 mL), and the combined organic fractions were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromotography (SiO_2; 5% EtOAc in CH_2Cl_2) to give catechol diacetate (**20**) (1.05 g, 26%, R_f 0.59), catechol monoacetate (**19**) (27.3 mg, 20%, R_f 0.32), and unreacted catechol (27.5 mg, 20%, R_f 0.22) as white solids.

Data for **19:** mp 57-58 °C (lit.[67] mp 57-58 °C); IR ($CHCl_3$ cast) 3600-3100 (br m), 1765 (s), 1741 (s), 1497 (s), 1232 (s), 1181 (s), 1172 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.12-7.03 (m, 2H, Ar-H), 6.97-6.85 (m, 2H, Ar-H), 5.83 (br s, 1H, OH), 2.32 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.80 ($C(O)CH_3$), 147.09 (*ipso*-C), 138.52 (*ipso*-C), 127.05 (CH), 122.49 (CH), 120.94 (CH), 117.70 (CH), 20.90 (CH_3); **MS** (EI) calcd for $C_8H_8O_3$ 152.0473, found 152.0471 (M^+, 19), 110.0370 (100); Anal. **Calcd** for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.34; H, 5.34.

Data for **20:** IR ($CHCl_3$ cast) 1774 (s), 1493 (s), 1244 (s), 1203 (s), 1186 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29-7.13 (m, 4H, Ar-H), 2.28 (s, 6H, 2 x CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.00 (2 x C(O)O), 142.01 (*ipso*-C), 126.72 (CH),

123.40 (CH), 20.53 (2 x CH_3); MS (EI) calcd for $C_{10}H_{10}O_4$ 194.0579 found 194.0579 (M^+, 3.3), 110.0368 (100).

Procedure B.[67] A solution of distilled thionyl catechol (**21**) (5.10 g, 32.7 mmol) in glacial acetic acid (13 mL) and pyridine (1 drop) was heated to reflux for 6 h. The solvent was removed *in vacuo* resulting in a 2:2:1 mixture of catechol : monoacetate : diacetate (3.39 g, 68%). The products were isolated in a similar manner as for **19** and have physical properties and spectra in good agreement with those previously mentioned.



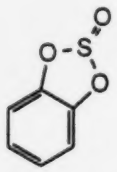
19a **20a**

Catechol [2-^{13}C]-Monoacetate (19a). Distilled triethylamine (3.82 mL, 27.4 mmol) was slowly added to a solution of catechol (2.88 g, 26.1 mmol) and [2-^{13}C]acetyl chloride (**22**) (2.07 g, 26.1 mmol) (isotopic purity 99% ^{13}C) in dry THF (100 mL). The same work-up procedure used in the preparation of **19** was employed to give catechol [2,2'-$^{13}C_2$]-diacetate (**20a**) (1.05 g, 26%, Rf 0.59), the monoacetate **19a** (1.34 g, 34%, Rf 0.32), and unreacted catechol (0.764 g, 19%) as white solids.

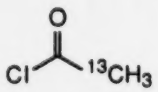
Data for **19a:** mp 56-57 °C; IR ($CHCl_3$ cast) 3600-3100 (br m), 1764 (m), 1740 (s), 1497 (m), 1233 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19-7.01 (m, 2H, Ar-H), 7.01-6.83 (m, 2H, Ar-H), 5.79 (br s, 1H, OH), 2.31 (d, 3H, J = 130.4 Hz, $^{13}CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.80 (d, J = 56.6 Hz, C(O)$^{13}CH_3$), 147.06 (*ipso*-C), 138.50 (*ipso*-C), 127.05 (CH), 122.48 (CH), 120.94 (CH), 117.70 (CH), 20.91 ($^{13}CH_3$); MS (EI) calcd for $^{13}C^{12}C_7H_8O_3$ 153.0507, found 153.0508 (M^+, 15), 110.0368 (100).

Data for **20a:** IR ($CHCl_3$ cast) 1775 (s), 1493 (m), 1245 (m), 1203 (s), 1167 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29-7.13 (m, 4H, Ar-H), 2.28 (d, 6H, J = 130.1 Hz,

2 x $^{13}C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.23 (d, J = 60.9 Hz, 2 x $\underline{C}(O)CH_3$), 142.13 (*ipso*-C), 126.60 ($\underline{C}H$), 123.44 ($\underline{C}H$), 20.60 (2 x $^{13}\underline{C}H_3$); MS (EI) calcd for $^{13}C_2{}^{12}C_8H_{10}O_4$ 196.0647 found 196.0648 (M^+, 4.1), 153.0508 (19), 110.0364 (100).

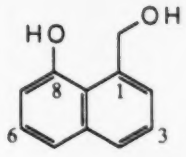


Thionyl Catechol (21).[67] A solution of distilled thionyl chloride (3.33 mL, 45.9 mmol) in dry Et_2O (15 mL) was slowly added to a solution of catechol (5.05 g, 45.9 mmol) and distilled pyridine (7.42 mL, 91.8 mmol) in dry Et_2O (25 mL). The mixture was heated to reflux for 8 h. After cooling, the solution was quenched by pouring into H_2O (75 mL). The organic layer was washed with H_2O (50 mL), and brine (20 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The resultant oil was distilled under reduced pressure to yield **21** (5.32 g, 74%) as an oil: bp 57-59 °C (1.75 mm Hg) [lit.[67] bp 137-138 °C (105 mm Hg)]; IR ($CHCl_3$ cast) 1475 (s), 1252 (m), 1220 (s), 817 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.22-7.06 (m, 4H, Ar-$\underline{H}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.74 (*ipso*-C),, 124.37 ($\underline{C}H$),, 112.42 ($\underline{C}H$),; MS (EI) calcd for $C_6H_4O_3S$ 155.9881 found 155.9889 (M^+, 96), 110.0366 (100); MS (CI, NH_3) 174 (MNH_4^+, 56), 156 (M^+, 100); Anal. Calcd for $C_6H_4O_3S$: C, 46.15; H, 2.58. Found: C, 45.94 H, 2.61.

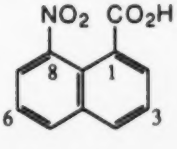


[2-^{13}C]Acetyl Chloride (22).[68] Sodium [2-^{13}C]-acetate (3.50 g, 42.7 mmol) (isotopic purity 99% ^{13}C) was carefully added to a flask containing phosphorus pentachloride (16.5 g, 79.1 mmol), and the mixture was then heated to 80 °C for 10 min and then cooled to room temperature. Distillation under a stream of argon gave **22**

(1.39 g, 42%): bp 52-54 °C (lit.[68] bp 52 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.68 (s, 3 H, $C\underline{H}_3$).

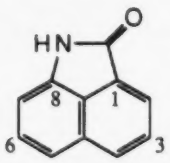


8-Hydroxy-1-naphthalenementhanol (23).[73] A modification of the procedure by Packer and Smith was employed.[73] A cooled (0 °C) solution of 1,8-naphtholactone (**27**) (10.0 g, 58.8 mmol) in distilled diglyme (100 mL) was treated with sodium borohydride (3.00 g, 79.3 mmol). After 0.5 h the reaction mixture was quenched with H_2O (600 mL) and acidified to pH 1 with 2N HCl. The white precipitate was collected and recrystallized from acetone-benzene to yield **23** (9.57 g, 93%) as colourless crystals: mp 144-145 °C (lit.[73] mp 144-146 °C); IR ($CHCl_3$ cast) 3413 (w), 2953 (m), 1583 (m), 1442 (m) 1292 (m), 1274 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$ + a few drops of CD_3OD) δ 10.3 (br s, 1H, OH) 7.74 (dd, 1H, *J* = 7.9, 1.7 Hz), 7.38 (dd, 1H, *J* = 8.3, 1.5 Hz, H-5), 7.32 (dd, 1H, *J* = 8.1, 7.3 Hz, H-6), 7.28 (dd, 1H, *J* = 7.8, 7.0 Hz, H-3), 7.22 (dd, 1H, *J* = 6.9, 1.6 Hz), 6.96 (dd, 1H, *J* = 7.3, 1.5 Hz, H-7), 5.55 (br s, 1H, OH), 4.98 (s, 2H, $HOC\underline{H}_2$); ^{13}C NMR (50 MHz, $CDCl_3$ + a few drops of CD_3OD) δ 152.96 (C-8), 136.38 (Ar-$\underline{C}$), 134.73 (Ar-$\underline{C}$), 129.25 ($\underline{C}$H), 127.19 ($\underline{C}$H), 126.27 ($\underline{C}$H), 125.14 ($\underline{C}$H), 123.57 (Ar-$\underline{C}$), 120.84 ($\underline{C}$H), 111.75 ($\underline{C}$H), 66.52 ($\underline{C}H_2$OH); MS (EI) calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0684 (M^+, 43), 155.0496 (100); Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.96; H, 5.81.



8-Nitro-1-naphthoic Acid (25).[69] A modification of the procedure by Koelsch and Hoffman was employed.[69] 1-Naphthoic acid (25.2 g, 146 mmol) was added to

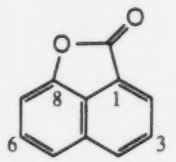
concentrated nitric acid (37 mL) and the mixture was heated to 65 °C emitting a yellowish vapour. Further heating to 85 °C produced a reddish vapour at which point the mixture was cooled to room temperature. After a yellowish solid had formed, H_2O (150 mL) was added and the solid was collected by filtration. This crude mixture of nitro acids was heated to reflux with ethanol (500 mL) for 2 h while a stream of hydrogen chloride gas was bubbled through the solution. The alcohol and excess hydrogen chloride were removed *in vacuo* and the yellowish residue was partitioned between Et_2O (300 mL) and 5% aqueous Na_2CO_3 (300 mL). The mixture was filtered and the ethereal layer was extracted with 5% aqueous Na_2CO_3 (2 x 50 mL). The combined aqueous layers were acidified with 2N HCl, and the yellow precipitate was collected by filtration to give **25** (15.3 g, 49%). Recrystallization from benzene and then from ethanol gave yellow crystals: mp 211-213 °C (dec) [lit.[69] mp 215 °C (dec)]; IR (KBr) 3430 (br m), 3300-2100 (br m), 1686 (s), 1527 (s), 1349 (s), 1279 (s) cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 11.2-10.2 (br s, 1H, COOH), 8.31 (dd, 1H, J = 8.2, 1.1 Hz), 8.27-8.12 (m, 3H), 7.74 (dd, 1H, J = 8.1, 7.3 Hz), 7.72 (dd, 1H, J = 8.1, 7.7 Hz); ^{13}C NMR (50 MHz, acetone-d_6) δ 168.36 (COOH), 148.70 (C-8), 135.76 (Ar-C), 135.06 (CH), 132.97 (CH), 132.12 (CH), 129.40 (Ar-C), 127.48 (CH), 126.24 (CH), 125.84 (CH), 122.41 (Ar-C); MS (EI) calcd for $C_{11}H_7NO_4$ 217.0375, found 217.0375 (M^+, 29), 171.0447 (100); Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 61.14; H, 3.53; N, 6.12.



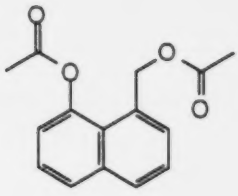
1,8-Naphtholactam (26).[72] Procedure A. The procedure of Birch *et al.* was employed.[72] A mixture of naphthalic anhydride (25.0 g, 126 mmol) and hydroxylamine hydrochloride (8.85 g, 127 mmol) in dry pyridine (200 ml) was heated to reflux for 1 h. Heating was discontinued and 4-toluenesulfonyl chloride (51.9 g, 272 mmol) was added

to cause controlled boiling and then the mixture was heated to reflux for 1 h. The red mixture was poured into H_2O (400 mL) and the brownish precipitate was collected by filtration and washed with 10% aqueous $NaHCO_3$ (200 mL) and H_2O (100 mL). The precipitate was heated to reflux in H_2O (290 mL) and ethanol (96 mL) containing NaOH (19 g) for 2 h, and during the second hour ethanol was distilled off the mixture. The solution was cooled, acidified with conc. HCl, and the yellowish-brown precipitate was collected by filtration, washed with H_2O and recrystallized from benzene to yield **26** (16.7 g, 78%) as pale yellow crystals: mp 180-181 °C (lit.[72] mp 182-184 °C); IR ($CHCl_3$ cast) 3195 (br m), 1698 (s), 788 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.20 (bs, 1H, NH), 8.11 (d, 1H, J = 7.1 Hz, H-3), 8.05 (d, 1H, J = 8.0 Hz, H-5), 7.74 (dd, 1H, J = 8.0, 7.1 Hz, H-4), 7.56 (d, 1H, J = 8.3 Hz, H-6), 7.45 (dd, 1H, J = 8.3, 6.8 Hz, H-7), 7.03 (d, 1H, J = 6.8 Hz, H-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.45 (CONH), 137.25 (C-8), 131.24 (CH), 129.47 (Ar-C), 128.70 (2 x CH), 126.82 (Ar-C), 126.38 (Ar-C), 124.44 (CH), 120.36 (CH), 106.73 (CH); MS (EI) calcd for $C_{11}H_7NO$: 169.0528, found 169.0525 (M^+, 100); Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.23. Found: C, 78.19; H, 4.24; N, 8.33.

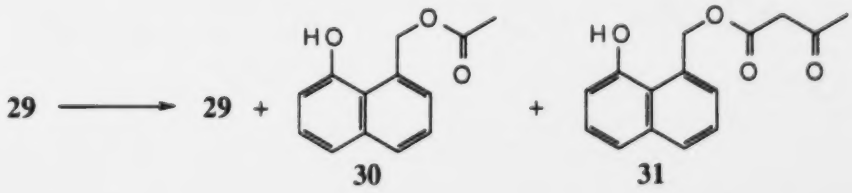
Procedure B. A modified procedure of Bamberger and Philip was adopted.[70] Concentrated HCl (2 mL) was added to 8-nitro-1-naphthoic acid **25** (498 mg, 2.29 mmol) and powdered tin (889 mg, 7.49 mmol), and the mixture was heated gently to 40 °C over 40 min. Et_2O (10 mL) was added to the slurry and the mixture was stirred at 40 °C for 12 h. The Et_2O layer was removed *via* pipette, and the reaction extracted similarly with a second portion of Et_2O. The combined Et_2O layers were washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid (337 mg, 87%). Recrystallization from benzene gave pale yellow crystals having physical and spectral properties in good agreement with those shown above.



1,8-Naphtholactone (27).[71,72] A modification of the procedure of Elliger was employed.[71] The lactam **26** (8.46 g, 50.0 mmol) was heated to reflux in 0.5N NaOH (400 mL) until dissolution was complete (45 min). The resulting solution was cooled to 0 °C and sodium nitrite (3.45 g, 50.0 mmol) was added. The mixture was added dropwise to a well stirred solution of H_2SO_4 (55 mL) in H_2O (1 L), and after the addition was complete, the acidic mixture was warmed gradually. At 40 °C gas evolution occurred with separation of a sticky solid. The reaction was heated further to 70 °C, then cooled to 0 °C, and extracted with EtOAc (4 x 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2; 50% EtOAc in hexane, R_f 0.64) of the tan solid yielded **27** (7.96 g, 94%) as a colourless solid: mp 104-105 °C (lit.[71] mp 105-107 °C); IR ($CHCl_3$ cast) 1795 (s), 1781 (s), 1748 (s), 1647 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.16 (d, 1H, J = 8.1 Hz, H-3), 8.13 (d, 1H, J = 7.1 Hz, H-5), 7.79 (dd, 1H, J = 8.1, 7.1 Hz, H-4), 7.67 (d, 1H, J = 8.3 Hz, H-6), 7.57 (dd, 1H, J = 8.3, 7.1 Hz, H-7), 7.15 (d, 1H, J = 7.1 Hz, H-8); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.03 (COO), 150.13 (C-8), 132.01 (CH), 129.87 (Ar-C), 129.50 (CH), 129.25 (CH), 128.92 (Ar-C), 126.23 (CH), 121.20 (Ar-C), 120.85 (CH), 105.98 (CH); MS (EI) calcd for $C_{11}H_6O_2$ 170.0368, found 170.0366 (M^+, 100); **Anal.** Calcd for $C_{11}H_6O_2$: C, 77.64; H, 3.55. Found: C, 77.65; H, 3.41.



8-Acetyloxy-1-naphthalenemethyl Acetate (29). Distilled acetyl chloride (0.58 mL, 8.20 mmol) was slowly added to a solution of **23** (0.572 g, 3.29 mmol) and triethylamine (1.19 mL, 8.54 mmol) in dry THF (30 mL). After stirring at room temperature for 30 min, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 100% CH_2Cl_2, R_f 0.33) to give **29** (0.838 g, 98%) as a colourless solid: mp 80-81 °C; IR ($CHCl_3$ cast) 2923 (w), 1767 (s), 1737 (s), 1368 (m), 1225 (s), 1194 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (dd, 1H, J = 8.0, 1.3 Hz), 7.74 (dd, 1H, J = 8.2, 1.2 Hz), 7.56 (dd, 1H, J = 7.1, 1.4 Hz), 7.46 (dd, 1H, J = 8.0, 7.6 Hz), 7.40 (dd, 1H, J = 8.2, 7.1 Hz), 7.21 (dd, 1H, J = 7.6, 1.2 Hz), 5.62 (s, 2H, $OC\underline{H}_2$), 2.41 (s, 3H, $C\underline{H}_3$), 2.04 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.74 ($\underline{C}(O)O$), 169.57 ($\underline{C}(O)O$), 146.45 (C-1), 136.12 (Ar-$\underline{C}$), 130.11 ($\underline{C}H$), 129.76 ($\underline{C}H$), 129.53 (Ar-$\underline{C}$), 127.12 ($\underline{C}H$), 125.57 ($\underline{C}H$), 125.43 ($\underline{C}H$), 125.24 (Ar-$\underline{C}$), 121.08 ($\underline{C}H$), 66.89 ($O\underline{C}H_2$), 21.60 ($\underline{C}H_3$), 20.85 ($\underline{C}H_3$); MS (EI) calcd for $C_{15}H_{14}O_4$ 258.0892, found 258.0907 (M^+, 10.45), 216.0786 (15), 155.0496 (100); Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.95; H, 5.43.



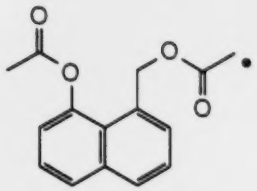
30 **31**

Condensation Reaction Using 8-Acetyloxy-1-naphthalenemethyl Acetate (29). A solution of **29** (178 mg, 0.689 mmol) in THF (4 mL) was slowly added to a cold (0 °C) solution of LHMDS (129 mg, 0.746 mmol) in dry THF (6 mL). After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature, poured onto cooled 1N HCl

(5 mL), and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (10 mL) and the combined Et_2O fractions were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 5% EtOAc in hexane) to give recovered starting material **29** (58.3 mg, 33%, *Rf* 0.50); 8-hydroxy-1-naphthalenemethyl acetate (**30**) (57.6 mg, 32%, *Rf* 0.30); and 8-hydroxy-1-naphthalenemethyl acetoacetate (**31**) (37.1 mg, 21%, *Rf* 0.17).

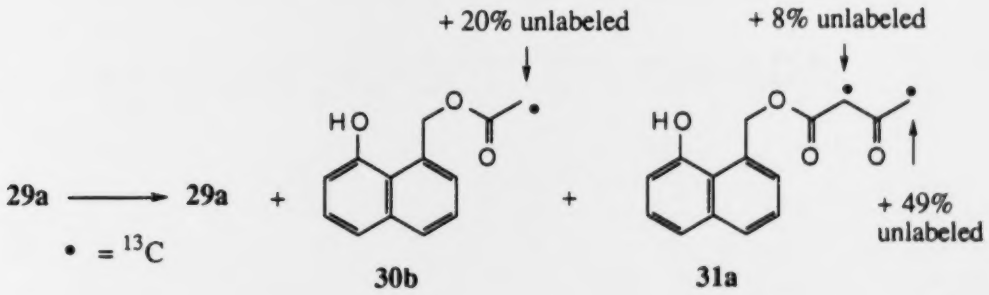
Data for **30:** mp 113-114 °C; IR ($CHCl_3$ cast) 3357 (s), 1718 (s), 1584 (m), 1385 (m), 1338 (m), 1283 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.71 (dd, 1H, *J* = 7.6, 1.9 Hz), 7.41 (dd, 1H, *J* = 7.5, 1.4 Hz), 7.35 (dd, 1H, *J* = 7.6, 7.5 Hz), 7.34 (dd, 1H, *J* = 8.2, 1.4 Hz), 7.25 (dd, 1H, *J* = 8.1, 7.3 Hz), 7.00 (br m, 1H, OH), 6.84 (dd, 1H, *J* = 7.3, 1.4 Hz), 5.88 (s, 2H, $OC\underline{H}_2$), 2.19 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.90 ($\underline{C}(O)O$), 153.34 (C-1), 136.34 (Ar-$\underline{C}$), 131.39 (Ar-$\underline{C}$), 128.99 ($\underline{C}H$), 126.52 ($\underline{C}H$), 126.17 ($\underline{C}H$), 125.50 ($\underline{C}H$), 122.75 (Ar-$\underline{C}$), 121.21 ($\underline{C}H$), 111.35 ($\underline{C}H$), 67.66 ($O\underline{C}H_2$), 21.34 ($\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{12}O_3$ 216.0786, found 216.0787 (M^+, 21), 156.0570 (100); Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.24; H, 5.45.

Data for **31:** mp 95-97 °C; IR ($CHCl_3$ cast) 3600-3100 (br m), 1731 (s), 1705 (s), 1280 (s), 1157 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (dd, 1H, *J* = 7.8, 1.7 Hz), 7.49-7.28 (m, 3H), 7.23 (dd, 1H, *J* = 8.0, 7.7 Hz), 7.00 (br s, 1H, OH), 6.88 (dd, 1H, *J* = 7.3, 1.3 Hz), 5.87 (s, 2H, $OC\underline{H}_2$), 3.54 (s, 2H, $C\underline{H}_2$), 2.23 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.91 ($\underline{C}(O)$), 167.43 ($\underline{C}(O)O$), 153.10 (C-1), 136.30 (Ar-$\underline{C}$) 130.72 (Ar-$\underline{C}$), 129.36 ($\underline{C}H$), 127.68 ($\underline{C}H$), 126.22 ($\underline{C}H$), 125.47 ($\underline{C}H$), 122.93 (Ar-$\underline{C}$), 121.31 ($\underline{C}H$), 111.68 ($\underline{C}H$), 68.83 ($O\underline{C}H_2$), 50.19 ($\underline{C}H_2$), 30.28 ($\underline{C}H_3$); MS (EI) calcd for $C_{15}H_{14}O_4$ 258.0892, found 258.0894 (M^+, 3.4), 156.0571 (100); Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.67; H, 5.57.



• = ^{13}C

8-Acetyloxy-1-naphthalenemethyl [2-^{13}C]-Acetate (29a). The same method as for the preparation of diacetate **29**. Thus, acylation of labeled monoacetate **30a** (0.517 g, 2.39 mmol) with acetyl chloride (0.203 mL, 2.87 mmol) afforded **29a** (0.613 g, 99%): mp 80-81 °C; IR ($CHCl_3$ cast) 1766 (s), 1737 (s), 1358 (s), 1224 (s), 1191 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.72 (dd, 1H, *J* = 8.1, 1.4 Hz), 7.56 (dd, 1H, *J* = 7.2, 1.4 Hz), 7.43 (dd, 1H, *J* = 7.9, 7.4 Hz), 7.40 (dd, 1H, *J* = 8.1, 7.2 Hz), 7.20 (dd, 1H, *J* = 7.4, 1.4 Hz), 5.64 (s, 2H, $OC\underline{H}_2$), 2.42 (s, 3H, $C\underline{H}_3$), 2.03 (d, 3H, *J* = 130.1 Hz, $^{13}C\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.66 (d, *J* = 59.7 Hz, $\underline{C}(O)^{13}CH_3$), 169.48 ($\underline{C}(O)O$), 146.48 (C-1), 136.12 (Ar-$\underline{C}$), 130.00 ($\underline{C}H$), 129.72 ($\underline{C}H$), 129.57 (Ar-$\underline{C}$), 127.07 ($\underline{C}H$), 125.55 ($\underline{C}H$), 125.40 ($\underline{C}H$), 125.24 (Ar-$\underline{C}$), 121.04 ($\underline{C}H$), 66.84 ($O\underline{C}H_2$), 21.55 ($\underline{C}H_3$), 20.80 ($^{13}\underline{C}H_3$); MS (EI) calcd for $^{13}C^{12}C_{14}H_{14}O_4$ 259.0926 found 259.0924 (M^+, 15), 217.0817 (17), 156.0573 (100); Anal. Calcd for $^{13}C^{12}C_{14}H_{14}O_4$: C, 69.83; H, 5.44. Found: C, 69.67; H, 5.67.

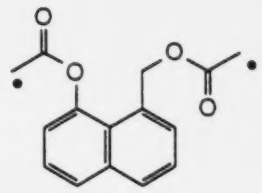


Condensation Reaction Using 8-Acetyloxy-1-naphthalenemethyl [2-^{13}C]-Acetate (29a). The same condensation procedure as for diacylated compound **32** was used. Thus, treatment of **29a** (80.2 mg, 0.311 mmol) with LHMDS (55.8 mg,

0.334 mmol) produced a residue, which after flash chromatography (SiO_2; 2% EtOAc in CH_2Cl_2) afforded the following: starting material **29a** (24.3 mg, 30%, *Rf* 0.58); a 4:1 mixture of 8-hydroxy-1-naphthalenemethyl [2-^{13}C]-acetate : 8-hydroxy-1-naphthalenemethyl acetate (**30b**) (30.6 mg, 38%, *Rf* 0.45); and 8-hydroxy-1-naphthalenemethyl [2,4-$^{13}C_2$]-acetoacetate (**31a**) (9.81 mg, 12%, *Rf* 0.22) which was 8% and 49% unlabeled in the C-2 methylene and C-4 methyl positions respectively.

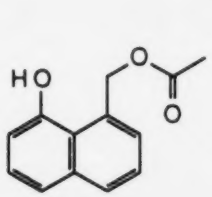
Data for 4:1 mixture, **30b:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd, 1H, *J* = 7.6, 1.9 Hz), 7.50 (dd, 1H, *J* = 7.5, 1.4 Hz), 7.43 (dd, 1H, *J* = 8.2, 1.4 Hz), 7.34 (dd, 1H, *J* = 7.6, 7.5 Hz), 7.30 (dd, 1H, *J* = 8.1, 7.3 Hz), 6.93 (dd, 1H, *J* = 7.3, 1.4 Hz), 6.83 (br s, 1H, OH), 5.89 (s, 2H, $OC\underline{H}_2$), 2.18 (d, 2.4H, *J* = 128.9 Hz, $^{13}C\underline{H}_3$), 2.18 (s, 0.6H, $^{12}C\underline{H}_3$); MS (EI) calcd for $^{13}C^{12}C_{12}H_{12}O_3$ 217.0820, found 217.0822 (M^+, 20), 156.0570 (100) and MS (EI) calcd for $C_{13}H_{12}O_3$ 216.0786, found 216.0784 (M^+, 3.8).

Data for **31a:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (dd, 1H, *J* = 7.8, 1.7 Hz), 7.49-7.28 (m, 3H), 7.23 (dd, 1H, *J* = 8.0, 7.7 Hz), 7.00 (br s, 1H, OH), 6.88 (dd, 1H, *J* = 7.3, 1.3 Hz), 5.87 (s, 2H, $OC\underline{H}_2$), 3.55 (d, 1.84H, *J* = 130.3 Hz, $^{13}C\underline{H}_2$), 3.55 (s, 0.16H, $^{12}C\underline{H}_2$), 2.24 (dd, 1.8H, *J* = 128.2, 1.53 Hz, $^{13}C\underline{H}_3$), 2.24 (d, 0.2H, *J* = 1.47 Hz, $^{12}C\underline{H}_3$, 39.2%); ^{13}C NMR (50 MHz, $CDCl_3$) the same as unlabeled **31** except, δ 50.23 (d, *J* = 14.0 Hz, C(O)$^{13}\underline{C}H_2$C(O)), 50.23 (s, C(O)$\underline{C}H_2$C(O)), 30.32 (d, *J* = 14.0 Hz, C(O)$^{13}\underline{C}H_3$), 30.32 (s, C(O)$\underline{C}H_3$); MS (EI) calcd for $^{13}C_2{}^{12}C_{13}H_{14}O_4$ 260. 0960 found 260.0963 (M^+, 2.1), and MS (EI) calcd for $^{13}C^{12}C_{14}H_{14}O_4$ 259.0926 found 259.0927 (M^+, 1.5), 156.0573 (100).

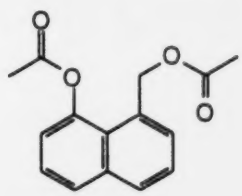


• = ^{13}C

8-[2-^{13}C]-Acetyloxy-1-naphthalenemethyl [2-^{13}C]-Acetate (29b). The same method as for the preparation of diacetate **29** was employed, except acetyl chloride was replaced by [2-^{13}C]acetyl chloride (**22**) (0.60 mL, 8.33 mmol) to convert the diol **23** (0.580 g, 3.33 mmol) to **29b** (0.696 g, 80%): mp 82-83 °C; IR ($CHCl_3$ cast) 1766 (s), 1737 (s), 1358 (s), 1224 (s), 1191 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.73 (dd, 1H, *J* = 8.1, 1.4 Hz), 7.55 (dd, 1H, *J* = 7.2, 1.4 Hz), 7.45 (dd, 1H, *J* = 7.9, 7.5 Hz), 7.41 (dd, 1H, *J* = 8.1, 7.2 Hz), 7.20 (dd, 1H, *J* = 7.5, 1.3 Hz), 5.63 (s, 2H, $OC\underline{H}_2$), 2.43 (d, 3H, *J* = 131.1 Hz, $^{13}C\underline{H}_3$), 2.06 (d, 3H, *J* = 130.1 Hz, $^{13}C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.66 (d, *J* = 58.1 Hz, $\underline{C}(O)^{13}CH_3$), 169.46 (d, *J* = 60.7 Hz, $\underline{C}(O)^{13}CH_3$), 146.45 (C-1), 136.10 (Ar-$\underline{C}$), 129.98 ($\underline{C}H$), 129.70, ($\underline{C}H$) 129.56 (Ar-$\underline{C}$), 127.06 ($\underline{C}H$), 125.53 ($\underline{C}H$), 125.35 ($\underline{C}H$), 125.22 (Ar-$\underline{C}$), 121.03 ($\underline{C}H$), 66.83 ($\underline{C}H_2$), 21.52 ($^{13}\underline{C}H_3$), 20.78 ($^{13}\underline{C}H_3$); MS (EI) calcd for $^{13}C_2{}^{12}C_{13}H_{14}O_4$ 260.0959 found 260.0960 (M^+, 11), 217.0819 (15), 156.0573 (100); Anal. Calcd for $^{13}C_2{}^{12}C_{13}H_{14}O_4$: C, 69.99; H, 5.42. Found: C, 69.89; H, 5.42.



30

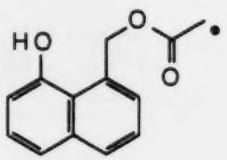


29

8-Hydroxy-1-naphthalenemethyl Acetate (30). Procedure A. Triethylamine (0.313 mL, 2.25 mmol) was added to a solution of diol **23** (0.36 g, 2.07 mmol) in dry Et_2O (5 mL) and THF (1 mL), and the mixture was heated to reflux for 5 min. After

cooling to room temperature, acetyl chloride (0.147 mL, 2.07 mmol) was added with stirring. The reaction mixture was heated to reflux for 3 h, over which time acetyl chloride was added as required (4 x 0.10 mL, 4 x 1.41 mmol) to obtain the best balance between reaction of the diol and overreaction to give the diacetate. The solution was cooled and the precipitate was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (SiO_2; 5% EtOAc in CH_2Cl_2) to give 8-acetyloxy-1-naphthalenemethyl acetate (**29**) (51.6 mg, 12%, *Rf* 0.50), the monoacetate **30** (0.267 g, 60%), and unreacted starting material **23** (30.7 mg, 7%, *Rf* 0.21) as colourless solids. The three products had physical and spectral properties in good agreement with those previously mentioned (see condensation reaction of diacetate **29**).

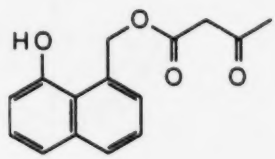
Procedure B. The same method was used as procedure A, except *N*,*N*-dimethylaniline (0.30 mL, 2.37 mmol) was employed instead of triethylamine. Thus, acylation of diol **23** (0.379 g, 2.18 mmol) produced **30** (0.391 g, 83%) and unreacted starting material **23** (31.4 mg, 7%) each having physical and spectral properties in good agreement with those previously mentioned.



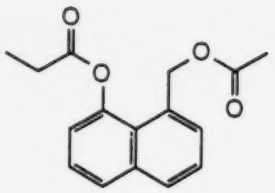
• = ^{13}C

8-Hydroxy-1-naphthalenemethyl [2-^{13}C]-Acetate (30a). The same method was employed as in procedure B for the preparation of unlabeled monoacetate **30** , except acetyl chloride were replaced by [2-^{13}C]acetyl chloride (**22**) (1.71 g, 21.8 mmol). Thus, diol **23** (3.79 g, 21.7 mmol) afforded a brown oil, which was purified by flash chromatography (SiO_2; 5% EtOAc in CH_2Cl_2, *Rf* 0.41) to yield 8-hydroxy-1-naphthalenemethyl [2-^{13}C]-acetate (**30a**) (2.44 g, 52%) as colourless crystals: mp 112-

113 °C; IR ($CHCl_3$ cast) 3359 (br s), 1718 (s), 1584 (m), 1365 (m), 1337 (m), 1284 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd, 1H, *J* = 7.6, 1.9 Hz), 7.50 (dd, 1H, *J* = 7.5, 1.4 Hz), 7.43 (dd, 1H, *J* = 8.1, 1.4 Hz), 7.34 (dd, 1H, *J* = 7.6, 7.5 Hz), 7.30 (dd, 1H, *J* = 8.1, 7.3 Hz), 6.93 (dd, 1H, *J* = 7.3, 1.4 Hz), 6.83 (br s, 1H, OH), 5.89 (s, 2H, $OC\underline{H}_2$), 2.23 (d, 3H, *J* = 128.9 Hz, $^{13}C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.01 (d, *J* = 59.6 Hz, $\underline{C}(O)^{13}CH_3$), 153.44 (C-1), 136.34 (Ar-$\underline{C}$), 131.48 (Ar-$\underline{C}$), 128.91 ($\underline{C}H$), 126.32 ($\underline{C}H$), 126.15 ($\underline{C}H$), 125.47 ($\underline{C}H$), 122.72 (Ar-$\underline{C}$), 121.09 ($\underline{C}H$), 111.23 ($\underline{C}H$), 67.67 ($O\underline{C}H_2$), 21.30 ($^{13}\underline{C}H_3$); MS (EI) calcd for $^{13}C^{12}C_{12}H_{12}O_3$ 217.0820, found 217.0822 (M^+, 20), 156.0570 (100); Anal. Calcd for $^{13}C^{12}C_{12}H_{12}O_3$: C, 72.33; H, 5.59. Found: C, 72.22; H, 5.74.

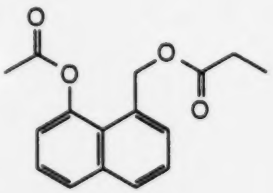


8-Hydroxy-1-naphthalenemethyl Acetoacetate (31). Distilled diketene (0.065 mL, 0.844 mmol) was added dropwise to a solution of diol **23** (0.144 g, 0.844 mmol) in dry THF (10 mL), followed by 2 drops of triethylamine. After stirring at room temperature for 5 min, the reaction mixture was heated to reflux for 10 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 10% EtOAc in hexane, R_f 0.51) to yield **31** (0.193 g, 89%) as clear crystals having physical and spectral properties in good agreement with those previously mentioned (see condensation of diacetate **29**).



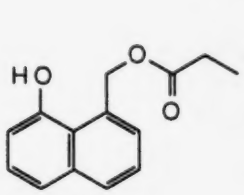
8-Acetyloxymethyl-1-naphthyl Propanoate (32). The same method as for the preparation of diacetate **29** was employed, except that acetyl chloride was replaced by propionyl chloride (0.482 mL, 5.54 mmol). Thus, monoacetate **30** (0.999 g, 4.62 mmol) afforded **32** (1.23 g, 97%): mp 73-74 °C; IR ($CHCl_3$ cast) 1764 (s), 1738 (s), 1225 (s), 1132 (s), 1118 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.80 (br d, 1H, *J* = 7.7 Hz), 7.72 (br d, *J* = 8.0 Hz), 7.56 (br d, 1H, *J* = 7.1 Hz), 7.44 (dd, 1H, *J* = 8.0, 7.4 Hz), 7.38 (dd, 1H, *J* = 7.7, 7.1 Hz), 7.18 (dd, 1H, *J* = 7.4, 1.5 Hz), 5.60 (s, 2H, $OC\underline{H}_2$), 2.63 (q, 2H, *J* = 7.2 Hz, $C\underline{H}_2CH_3$), 2.01 (s, 3H, $C\underline{H}_3$), 1.30 (t, 3H, *J* = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.96 ($\underline{C}(O)O$), 170.62 ($\underline{C}(O)O$), 146.64 (C-1), 136.09 (Ar-$\underline{C}$), 129.64 (2 x $\underline{C}H$ & Ar-$\underline{C}$), 126.90 ($\underline{C}H$), 125.46 ($\underline{C}H$), 125.36 ($\underline{C}H$), 125.21 (Ar-$\underline{C}$), 120.90 ($\underline{C}H$), 66.75 ($O\underline{C}H_2$), 28.05 ($\underline{C}H_2CH_3$), 20.80 ($\underline{C}H_3$), 8.85 ($CH_2\underline{C}H_3$); MS (EI) calcd for $C_{16}H_{16}O_4$ 272.1048, found 272.1047 (M^+, 10), 216.0786 (15), 156.0572 (100); Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.67; H, 6.01.

The condensation reaction using this material can be found after formation of compound **34**.

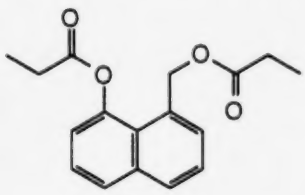


8-Acetyloxy-1-naphthalenemethyl Propanoate (33). The same method as for the preparation of diacetate **29** was employed. Thus, acylation of monopropanoate ester **34** (0.526 g, 2.28 mmol) with acetyl chloride (0.19 mL, 2.74 mmol) afforded **33** (0.607 g,

98%): mp 53-54 °C; IR ($CHCl_3$ cast) 2980 (w), 1768 (s), 1736 (s), 1196 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (br d, 1H, J = 7.8 Hz), 7.74 (br d, J = 8.0 Hz), 7.58 (br d, 1H, J = 7.0 Hz), 7.45 (dd, 1H, J = 8.0, 7.3 Hz), 7.41 (dd, 1H, J = 7.8, 7.0 Hz), 7.21 (dd, 1H, J = 7.3, 1.5 Hz), 5.63 (s, 2H, $OC\underline{H}_2$), 2.42 (s, 3H, $C\underline{H}_3$), 2.33 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 1.06 (t, 3H, J = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.15 ($\underline{C}(O)O$), 169.46 ($\underline{C}(O)O$), 146.45 (C-1), 136.08 (Ar-$\underline{C}$), 129.77 ($\underline{C}H$), 129.58 ($\underline{C}H$ & Ar-$\underline{C}$), 127.03 ($\underline{C}H$), 125.53 ($\underline{C}H$), 125.32 ($\underline{C}H$), 125.17 (Ar-$\underline{C}$), 120.95 ($\underline{C}H$), 66.62 ($O\underline{C}H_2$), 27.33 ($\underline{C}H_2CH_3$), 21.54 ($\underline{C}H_3$), 8.85 ($CH_2\underline{C}H_3$); MS (EI) calcd for $C_{16}H_{16}O_4$ 272.1048, found 272.1049 (M^+, 10), 230.0941 (12), 156.0576 (100); Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.34; H, 5.95.



34



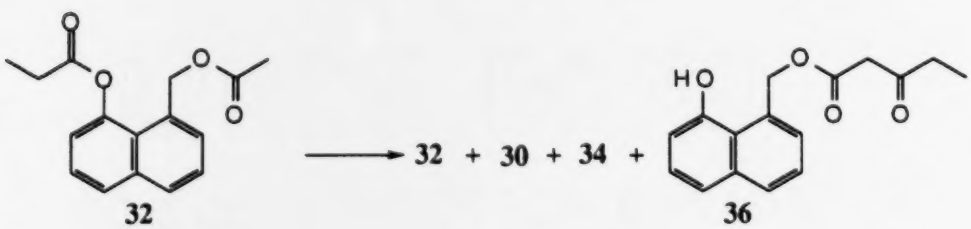
35

8-Hydroxy-1-naphthalenemethyl Propanoate (34). The same method as for the preparation of diacetate **29** was employed, except that acetyl chloride was replaced propionyl chloride (0.495 mL, 5.70 mmol). Thus, acylation of diol **23** (0.992 g, 5.70 mmol) afforded a residue, which after flash chromatography (SiO_2; 5% EtOAc in CH_2Cl_2) produced two products: 8-propanoyloxy-1-naphthalenemethyl propanoate (**35**) (0.277 g, 21%, R_f 0.70), and the desired 8-hydroxy-1-naphthalenemethyl propanoate (**34**) (0.853 g, 65%, R_f 0.30) as colourless solids.

Data for **34:** mp 107-108 °C; IR ($CHCl_3$ cast) 3348 (s), 1720 (s), 1711 (s), 1583 (s), 1337 (s), 1282 (s), 1212 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd, 1H, J = 7.8, 1.6 Hz), 7.50 (dd, 1H, J = 8.0, 1.5 Hz, H-4), 7.45-7.22 (m, 3H), 7.30-7.20 (br s, 1H, OH), 6.95 (dd, 1H, J = 7.3, 1.6 Hz, H-2), 5.90 (s, 2H, $OC\underline{H}_2$), 2.47 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 1.22 (t, 3H, J = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.42

(C(O)O), 153.54 (C-1), 136.31 (Ar-C), 131.60 (Ar-C), 128.64 (CH), 126.20 (CH), 125.98 (CH), 125.47 (CH), 122.71 (Ar-C), 121.05 (CH), 111.27 (CH), 67.51 (OCH_2), 27.99 (CH_2CH_3), 9.21 (CH_2CH_3); MS (EI) calcd for $C_{14}H_{14}O_3$ 230.0940, found 230.0941 (M^+, 20), 156.0573 (100); Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.17; H, 6.33.

Data for **35:** mp 70-72 °C; IR ($CHCl_3$ cast) 2980 (w), 1765 (s), 1736 (s), 1182 (s), 1132 (s), 1118 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (br d, 1H, *J* = 7.8 Hz), 7.70 (br d, *J* = 8.0 Hz), 7.56 (br d, 1H, *J* = 7.0 Hz), 7.42 (dd, 1H, *J* = 8.0, 7.3 Hz), 7.38 (dd, 1H, *J* = 7.8, 7.0 Hz), 7.18 (br d, 1H, *J* = 7.4 Hz), 5.59 (s, 2H, OCH_2), 2.62 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 2.31 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 1.29 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 1.08 (t, 3H, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.09 (C(O)O), 172.92 (C(O)O), 146.61 (C-1), 136.03 (Ar-C), 129.75 (Ar-C), 129.46 (2 x CH), 126.86 (CH), 125.46 (CH), 125.30 (CH), 125.13 (CH), 120.81 (CH), 66.52 (OCH_2), 28.01 (CH_2CH_3), 27.30 (CH_2CH_3), 8.81 (2 x CH_2CH_3); MS (EI) calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1206 (M^+, 7), 230.0941 (11), 156.0572 (100); Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.39; H, 6.32.

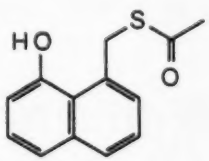


32 **36**

Condensation Reaction Using 8-Acetyloxymethyl-1-naphthyl Propanoate (32). A solution of **32** (0.187 g, 0.685 mmol) in dry THF (5 mL) was slowly added to a cold (-78 °C) solution of LHMDS (0.130 g, 0.753 mmol) in dry THF (20 mL). After stirring at -78 °C for 30 min, the reaction mixture was poured into cooled 1N HCl and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (10 mL) and the combined Et_2O fractions were washed with H_2O (10 mL) and brine (10 mL), dried

($MgSO_4$) and concentrated *in vacuo*. The resultant orange residue was purified by flash chromatography (SiO_2; 2% EtOAc in CH_2Cl_2) to give unreacted starting material **32** (62.6 mg, 34%, R_f 0.33), 8-hydroxy-1-naphthalenemethyl propanoate (**34**) (7.88 mg, 4%, R_f 0.23), 8-hydroxy-1-naphthalenemethyl acetate (**30**) (22.1 mg, 12%, R_f 0.10), and 8-hydroxy-1-naphthalenemethyl 3-oxopentanoate (**36**) (55.2 mg, 30%, R_f 0.07). The first three products obtained above had physical and spectral properties in good agreement with those previously mentioned.

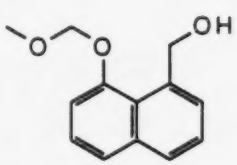
Data for **36:** IR ($CHCl_3$ cast) 3600-3000 (br s), 3050 (m), 2980 (m), 1734 (s), 1706 (s), 1585 (m), 1281 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (dd, 1H, J = 7.9, 1.7 Hz), 7.47-7.20 (m, 4H), 7.04 (br s, 1H, OH), 6.88 (dd, 1H, J = 7.3, 1.5 Hz), 5.94 (s, 2H, $OC\underline{H}_2$), 3.50 (s, 2H, $C\underline{H}_2$), 2.52 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 1.02 (t, 3H, J = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.46 ($\underline{C}$(O)), 167.58 ($\underline{C}$(O)O), 153.13 (C-1), 136.29 (Ar-$\underline{C}$), 130.82 (Ar-$\underline{C}$), 129.29 ($\underline{C}$H), 127.52 ($\underline{C}$H), 126.20 ($\underline{C}$H), 125.43 ($\underline{C}$H), 122.96 (Ar-$\underline{C}$), 121.26 ($\underline{C}$H), 111.71 ($\underline{C}$H), 66.75 ($O\underline{C}H_2$), 49.01 ($\underline{C}H_2$), 36.50 ($\underline{C}H_2CH_3$), 7.48 ($CH_2\underline{C}H_3$); MS (CI, NH_3) 290 (MNH_4^+, 52), 272 (24), 157 (100).



8-Hydroxy-1-naphthalenemethyl Thioacetate (37). Procedure A. A solution of protected thioester **39** (29.7 mg, 0.108 mmol) in H_2O (2 mL), 6 M HCl (5 mL) and THF (7 mL) was heated to 54 °C for 3 h. After cooling, the aqueous layer was extracted with Et_2O (2 x 20 mL), and the combined organic fractions were washed with H_2O (10 mL) and brine (10 mL), then dried ($MgSO_4$), and concentrated *in vacuo*. The resultant green oil was purified by flash chromatography (SiO_2; 50% EtOAc in hexane, R_f 0.58) to give 8-hydroxy-1-naphthalenemethyl thioacetate (**37**) (20.0 mg, 80%): IR ($CHCl_3$ cast) 3600-3100 (br m), 1647 (s), 1581 (m), 1352 (m), 1283 (m), 1128 (m), 1118

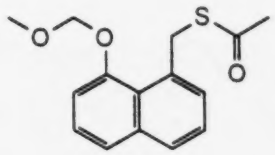
(m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (dd, 1H, *J* = 8.2, 1.4 Hz), 7.51 (dd, 1H, *J* = 7.2, 1.4 Hz), 7.43 (dd, 1H, *J* = 8.3, 1.2 Hz), 7.34 (dd, 1H, *J* = 8.2, 7.2 Hz), 7.27 (dd, 1H, *J* = 8.3, 7.5 Hz), 6.79 (dd, 1H, *J* = 7.5, 1.2 Hz), 4.86 (s, 2H, $SC\underline{H}_2$), 2.27 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.21 ($\underline{C}(O)S$), 153.17 (C-1), 136.56 (Ar-$\underline{C}$), 134.28 (Ar-$\underline{C}$), 128.15 ($\underline{C}H$), 128.10 ($\underline{C}H$), 125.92 ($\underline{C}H$), 125.64 ($\underline{C}H$), 122.56 (Ar-$\underline{C}$), 120.50 ($\underline{C}H$), 110.18 ($\underline{C}H$), 35.39 ($S\underline{C}H_2$), 30.16 ($\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{12}O_2S$ 232.0557, found 232.0555 (M^+, 44), 190.0450 (72), 156.0572 (100); Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.41; H, 5.44.

Procedure B. The same method as for the preparation of protected thioester **39** was employed. Thus, reaction of diol **23** (0.273 g, 1.57 mmol) with diisopropyl azodicarboxylate (0.618 mL, 3.14 mmol), triphenyl phosphine (0.828 g, 3.14 mmol), and thioacetic acid (0.224 mL, 3.14 mmol) afforded **37** (0.234 g, 64%) as a yellow solid with physical and spectral properties in good agreement with those quoted above.

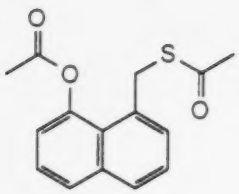


8-Methoxymethoxy-1-naphthalenemethanol (38). *n*-BuLi (1.5 M in hexanes, 0.354 mL, 0.532 mmol) was added to a cooled solution (-78 °C) of diol **23** (92.6 mg, 0.532 mmol) in dry THF (10 mL). Chloromethyl methyl ether (0.040 mL, 0.532 mmol) was then added slowly, and the reaction mixture was allowed to warm to room temperature. The mixture was diluted with Et_2O (20 mL) and washed quickly with 1N HCl (10 mL) and H_2O (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 25% EtOAc in hexane) to give the desired product **38** (46.5 mg, 40%): IR ($CHCl_3$ cast) 3600-3000 (br m), 3054 (m), 2995 (m), 2897 (m), 2826 (m), 1583 (s), 1155 (s), 1041 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd, 1H, *J* = 7.2, 2.3 Hz), 7.56 (dd, 1H, *J* = 8.1, 1.2 Hz), 7.47 (dd, 1H, *J* = 7.0,

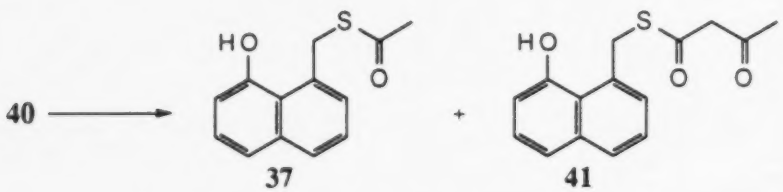
2.3 Hz), 7.41 (dd, 1H, J = 7.2, 7.0 Hz), 7.39 (dd, 1H, J = 8.0, 7.8 Hz), 7.18 (dd, 1H, J = 7.7, 1.2 Hz), 5.43 (s, 2H, OC$\underline{H}_2$O), 5.13 (s, 2H, OC$\underline{H}_2$Ar), 3.75 (s, 3H, OC$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.55 (C-1), 136.56 (Ar-$\underline{C}$), 136.29 (Ar-$\underline{C}$), 128.68 ($\underline{C}$H), 127.88 ($\underline{C}$H), 125.98 ($\underline{C}$H), 125.65 ($\underline{C}$H), 123.96 (Ar-$\underline{C}$), 123.21 ($\underline{C}$H), 109.83 ($\underline{C}$H), 95.54 (O$\underline{C}$H$_2$O), 66.88 (O$\underline{C}$H$_2$), 56.77 (O$\underline{C}$H$_3$); MS (EI) calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0943 (M^+, 17), 186.0678 (26), 156.0562 (100).



8-Methoxymethoxy-1-naphthalenemethyl Thioacetate (39). A modification of the procedure of Mitsunobu and Egushi was adopted.[75b] Diisopropyl azodicarboxylate (0.084 mL, 0.426 mmol) was added to a cooled solution (0 °C) of triphenylphosphine (113 mg, 0.426 mmol) in dry THF (2 mL). After 30 min, a solution of monoprotected alcohol **38** (46.5 mg, 0.212 mmol) and thioacetic acid (0.030 mL, 0.426 mmol) in THF (1 mL) was slowly added to the reaction mixture and the solution was stirred for an additional hour at 0 °C. The mixture was warmed to room temperature and concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography (SiO_2; 50% EtOAc in hexane, R_f 0.62) to produce **39** (38.3 mg, 65%): IR ($CHCl_3$ cast) 1685 (s), 1580 (m), 1435 (m), 1042 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (dd, 1H, J = 8.0, 1.5 Hz), 7.68 (dd, 1H, J = 7.3, 1.4 Hz), 7.55-7.27 (m, 3H), 7.17 (dd, 1H, J = 8.2, 1.5 Hz), 5.34 (s, 2H, OC$\underline{H}_2$O), 4.82 (s, 2H, SC$\underline{H}_2$), 3.57 (s, 3H, OC$\underline{H}_3$), 2.25 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 195.85 ($\underline{C}$(O)S), 154.39 (C-1), 136.28 (Ar-$\underline{C}$), 133.70 (Ar-$\underline{C}$), 129.54 ($\underline{C}$H), 128.35 ($\underline{C}$H), 125.65 ($\underline{C}$H), 125.60 ($\underline{C}$H), 123.66 (Ar-$\underline{C}$), 122.63 ($\underline{C}$H), 109.29 ($\underline{C}$H), 94.95 (O$\underline{C}$H$_2$O), 56.44 (O$\underline{C}$H$_3$), 35.86 (S$\underline{C}$H$_2$), 30.24 (C(O)$\underline{C}$H$_3$); MS (EI) calcd for $C_{15}H_{16}O_3S$ 276.0820, found 276.0817 (M^+, 25), 202.0445 (76), 155.0492 (100).



8-Acetyloxy-1-naphthalenemethyl Thioacetate (40). The same method as for the preparation of diacetate **29** was employed. Thus, acylation of thioester **37** (0.206 g, 0.887 mmol) with acetyl chloride (0.069 mL, 0.976 mmol) afforded **40** (0.183 g, 83%) as a yellow solid: mp 98-99 °C; IR ($CHCl_3$ cast) 1767 (s), 1687 (s), 1192 (s), 1113 (m), 767 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.74 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.56 (dd, 1H, *J* = 7.2, 1.5 Hz), 7.45 (dd, 1H, *J* = 7.9, 7.4 Hz), 7.37 (dd, 1H, *J* = 8.0, 7.2 Hz), 7.22 (dd, 1H, *J* = 7.4, 1.4 Hz), 4.66 (s, 2H, $SC\underline{H}_2$), 2.43 (s, 3H, $C\underline{H}_3$), 2.32 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 195.30 ($\underline{C}(O)S$), 169.38 ($\underline{C}(O)O$), 146.35 (C-1), 136.38 (Ar-$\underline{C}$), 131.51 (Ar-$\underline{C}$), 130.54 ($\underline{C}H$), 128.99 ($\underline{C}H$), 127.32 ($\underline{C}H$), 125.90 ($\underline{C}H$), 125.32 ($\underline{C}H$), 124.80 (Ar-$\underline{C}$), 120.79 ($\underline{C}H$), 34.88 ($S\underline{C}H_2$), 30.35 ($\underline{C}H_3$), 21.79 ($\underline{C}H_3$); MS (EI) calcd for $C_{15}H_{14}O_3S$ 274.0664, found 274.0661 (M^+, 23), 232.0556 (78), 190.0450 (100); Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14. Found: C, 65.70; H, 5.37.



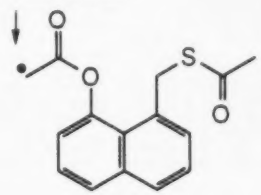
37 41

Condensation Reaction Using 8-Acetyloxy-1-naphthalenemethyl Thioacetate (40). The same method as for the condensation of diacylated compound **32** was employed, except the reaction mixture was allowed to warm to room temperature before quenching. Thus, treatment of **40** (31.2 mg, 0.114 mmol) with LHMDS (19.5 mg, 0.116 mmol) gave the 8-hydroxy-1-naphthalenemethyl thioacetate (**37**) (12.6 mg, 40%,

R_f 0.33), and 8-hydroxy-1-naphthalenemethyl thioacetoacetate (**41**) (9.8 mg, 31%, R_f 0.17). Physical and spectral properties of the monoacetate **37** were in good agreement with those previously described.

Data for **41:** IR ($CHCl_3$ cast) 3600-3000 (br m), 3050 (w), 2960 (w), 2920 (w), 1708 (s), 1660 (s), 1581 (s), 1282 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (dd, 1H, *J* = 8.1, 1.4 Hz), 7.50 (dd, 1H, *J* = 7.2, 1.4 Hz), 7.42 (dd, 1H, *J* = 8.2, 1.2 Hz), 7.34 (dd, 1H, *J* = 8.1, 7.2 Hz), 7.26 (dd, 1H, *J* = 8.2, 7.5 Hz), 6.78 (dd, 1H, *J* = 7.5, 1.2 Hz), 4.88 (s, 2H, $SC\underline{H}_2$), 3.62 (s, 2H, $C\underline{H}_2$), 2.22 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.81 ($\underline{C}(O)$), 192.43 ($\underline{C}(O)S$), 152.53 (C-1), 136.64 (Ar-$\underline{C}$), 133.26 (Ar-$\underline{C}$), 129.21 ($\underline{C}H$), 128.48 ($\underline{C}H$), 126.01 ($\underline{C}H$), 125.87 ($\underline{C}H$), 122.30 (Ar-$\underline{C}$), 121.90 ($\underline{C}H$), 110.95 ($\underline{C}H$), 58.17 ($\underline{C}H_2$), 35.90 ($S\underline{C}H_2$), 30.34 ($\underline{C}H_3$); MS (EI) calcd for $C_{15}H_{14}O_3S$ 274.0664, found 274.0664 (M^+, 10), 190.0451 (67), 156.0570 (100).

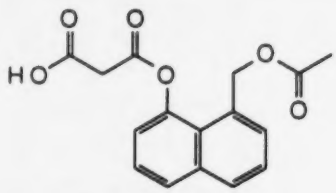
+ 26% unlabeled



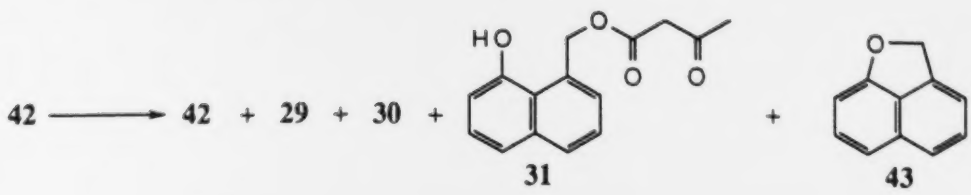
• = ^{13}C

8-[2-^{13}C]-Acetyloxy-1-naphthalenemethyl Thioacetate (40a). The same method as for the preparation of diacetate **29** was employed, except [2-^{13}C]acetyl chloride (**22**) (0.083 mL, 1.17 mmol) (isotopic purity 99% ^{13}C) was used. Thus, acylation of thioester **37** (0.226 g, 0.972 mmol) afforded **40a** (0.169 g, 63%), which was 26% unlabeled at the C-2 methyl group of the ring acetyl moiety: mp 98-99 °C; IR ($CHCl_3$ cast) 3080 (w), 2960 (w), 1766 (s), 1685 (s), 1186 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.79 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.75 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.57 (dd, 1H, *J* = 7.2, 1.5 Hz), 7.48 (dd, 1H, *J* = 7.9, 7.4 Hz), 7.39 (dd, 1H, *J* = 8.0, 7.2 Hz), 7.24 (dd, 1H, *J* = 7.4, 1.4 Hz), 4.68 (s, 2H, $SC\underline{H}_2$), 2.45 (d, 2.2H, *J* = 129.7 Hz, $^{13}C\underline{H}_3$), 2.45 (s, 0.8 H,

$^{12}C\underline{H}_2$), 2.32 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 195.03 ($\underline{C}(O)S$), 169.13 (d, J = 60.5 Hz, $\underline{C}(O)^{13}CH_3$), 169.13 (s, $\underline{C}(O)^{12}CH_3$), 146.47 (C-1), 136.39 (Ar-$\underline{C}$), 131.52 (Ar-$\underline{C}$), 130.45 ($\underline{C}H$), 128.90 ($\underline{C}H$), 127.20 ($\underline{C}H$), 125.80 ($\underline{C}H$), 125.26 ($\underline{C}H$), 124.87 (Ar-$\underline{C}$), 120.71 ($\underline{C}H$), 34.83 ($\underline{C}H_2S$), 30.22 ($\underline{C}H_3$), 21.65 ($^{13}\underline{C}H_3$); MS (EI) calcd for $^{13}C^{12}C_{14}H_{14}O_3S$ 275.0697, found 275.0699 (M^+, 16), 274.0665 (4.2), 232.0555 (81), 190.0451 (100); Anal. Calcd for $^{13}C^{12}C_{14}H_{14}O_3S$: C, 65.80; H, 5.13. Found: C, 65.49; H, 4.85.



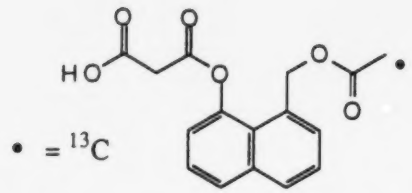
8-Acetyloxymethyl-1-naphthyl Malonate (42). The same method as used in the preparation of malonate derivative **16** was employed. Thus, condensation of monoacetate **30** (3.58 g, 16.6 mmol) with malonic monchloride (**15**) (3.47 g, 28.3 mmol) afforded **42** (4.80 g, 96%): mp 130.0-130.5 °C; IR ($CHCl_3$ cast) 3600-2700 (br m), 1766 (s), 1743 (s), 1705 (s), 1241 (s), 1135 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + a few drops of CD_3OD) δ 7.85 (dd, 1H, J = 8.1, 1.3 Hz), 7.78 (dd, 1H, J = 8.2, 1.2 Hz), 7.58 (dd, 1H, J = 7.1, 1.3 Hz), 7.48 (dd, 1H, J = 8.0, 7.7 Hz), 7.42 (dd, 1H, J = 8.2, 7.1 Hz), 7.31 (dd, 1H, J = 7.7, 1.3 Hz), 5.63 (s, 2H, $OC\underline{H}_2$), 3.76 (s, 2H, $C\underline{H}_2$), 2.03 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$ + a few drops of CD_3OD) δ 171.19 ($\underline{C}(O)O$), 168.46 ($\underline{C}(O)O$), 165.90 ($\underline{C}(O)O$), 146.23 (C-1), 136.11 (Ar-$\underline{C}$), 130.72 ($\underline{C}H$), 129.67 ($\underline{C}H$), 129.25 (Ar-$\underline{C}$), 127.48 ($\underline{C}H$), 125.65 ($\underline{C}H$), 125.46 ($\underline{C}H$), 125.06 (Ar-$\underline{C}$), 120.94 ($\underline{C}H$), 66.89 ($O\underline{C}H_2$), 41.74 ($\underline{C}H_2$), 20.79 ($\underline{C}H_3$); MS (CI, NH_3) 320 (MNH_4^+, 7), 319 (20), 302 (7), 157 (100); MS (EI) calcd for $C_{16}H_{14}O_6$ 302.0790, found 302.0784 (M^+, 0.26), 258.0890 (3.6), 216.0788 (14), 156.0570 (100); Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.24; H, 4.50.



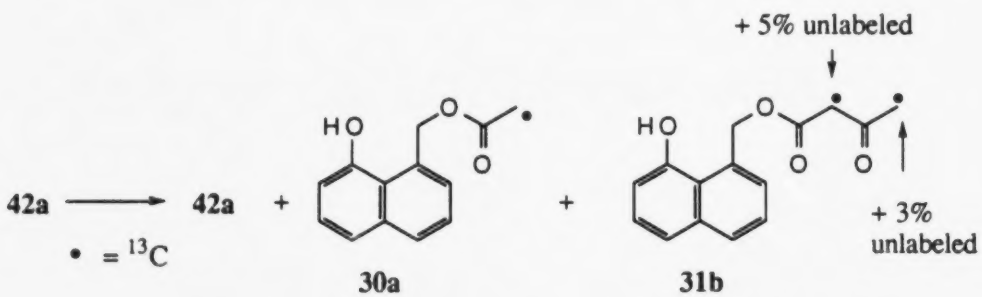
31 43

Condensation Reaction Using 8-Acetyloxymethyl-1-naphthyl Malonate (42). A solution of **42** (0.275 g, 0.909 mmol) in dry THF (5 mL) was slowly added to a cooled (-78 °C) solution of LHMDS (0.318 g, 1.90 mmol) in dry THF (10 mL). After stirring at room temperature for 3 h, the reaction mixture was heated to reflux for 1 h, then stirred overnight at room temperature. The mixture was poured into 1N HCl (5 mL) and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (10 mL), and the combined Et_2O fractions were washed with H_2O (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 25% EtOAc in hexane + 1% formic acid) to afford 2H-naphtho-[1,8-bc]-furan (**43**) (67.2 mg, 29%, *Rf* 0.58), 8-acetyloxy-1-naphthalenemethyl acetate (**29**) (3.6 mg, 2%, *Rf* 0.27), 8-hydroxy-1-naphthalenemethyl acetate (**30**) (20.8 mg, 9%, *Rf* 0.21), 8-hydroxy-1-naphthalenemethyl acetoacetate (**31**) (25.3 mg, 11%, *Rf* 0.12), and starting material **42** (52.2 mg, 22%, *Rf* 0.05). The products **29**, **30**, **31**, and **42** had physical and spectral properties in good agreement with previously quoted data.

Data for 2H-naphtho-[1,8-bc]-furan (**43**): mp 53-54 °C (lit.[76] mp 53-54 °C); IR ($CHCl_3$ cast) 2920 (w), 1620 (m), 1595 (m), 1487 (m), 1465 (m), 1382 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.64 (br d, 1H, *J* = 8.1 Hz), 7.51 (dd, 1H, *J* = 8.1, 6.9 Hz), 7.40 (dd, 1H, *J* = 8.3, 7.6 Hz), 7.26 (br d, 1H, *J* = 8.3 Hz), 7.23 (br d, 1H, *J* = 6.9 Hz), 6.74 (br d, 1H, *J* = 7.6 Hz), 5.78 (s, 2H, $OC\underline{H}_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.08 (C-1), 138.78 (Ar-<u>C</u>), 131.94 (Ar-<u>C</u>), 129.62 (<u>C</u>H), 128.74 (Ar-<u>C</u>), 128.56 (<u>C</u>H), 122.85 (<u>C</u>H), 115.36 (<u>C</u>H), 115.22 (<u>C</u>H), 100.73 (<u>C</u>H), 77.06 ($O\underline{C}H_2$); MS (EI) calcd for $C_{11}H_8O$ 156.0575, found 156.0572 (100), 155.0496 (78).



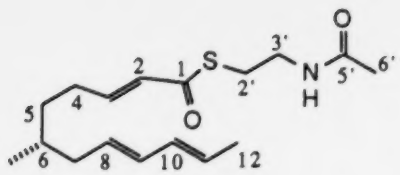
8-[2-^{13}C]-Acetyloxymethyl-1-naphthyl Malonate (42a). The same method as used in the preparation of malonate derivative **16** was employed. Thus, condensation of [2-^{13}C]-labeled monoacetate **30a** (0.601 g, 2.77 mmol) with malonic monchloride (**15**) (0.682 g, 5.57 mmol) afforded **42a** (0.779 g, 93%): mp 129-130 °C; IR ($CHCl_3$ cast) 3600-3100 (br s), 1768 (m), 1743 (m), 1707 (m), 1136 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$ + a few drops of CD_3OD) δ 7.84 (dd, 1H, *J* = 8.1, 1.3 Hz), 7.77 (dd, 1H, *J* = 8.1, 1.2 Hz), 7.60 (dd, 1H, *J* = 7.1, 1.3 Hz), 7.47 (dd, 1H, *J* = 8.1, 7.7 Hz), 7.41 (dd, 1H, *J* = 8.1, 7.1 Hz), 7.30 (dd, 1H, *J* = 7.7, 1.3 Hz), 5.62 (s, 2H, $OC\underline{H}_2$), 3.76 (s, 2H, $C\underline{H}_2$), 2.04 (d, 3H, *J* = 130.9 Hz, $^{13}C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$ + a few drops of CD_3OD) δ 171.22 (d, *J* = 59.4 Hz, $\underline{C}(O)^{13}CH_3$), 168.39 ($\underline{C}(O)O$), 165.96 ($\underline{C}(O)O$), 146.23 (C-1), 136.09 (Ar-$\underline{C}$), 130.72 ($\underline{C}H$), 129.67 ($\underline{C}H$), 129.24 (Ar-$\underline{C}$), 127.46 ($\underline{C}H$), 125.64 ($\underline{C}H$), 125.46 ($\underline{C}H$), 125.06 (Ar-$\underline{C}$), 120.94 ($\underline{C}H$), 66.89 ($O\underline{C}H_2$), 41.74 ($\underline{C}H_2$), 20.79 ($^{13}\underline{C}H_3$); MS (CI, NH_3) 321 (MNH_4^+, 5), 320 (14), 157 (100); Anal. Calcd for $^{13}C^{12}C_{15}H_{14}O_6$: C, 63.69; H, 4.65. Found: C, 63.79; H, 4.86.



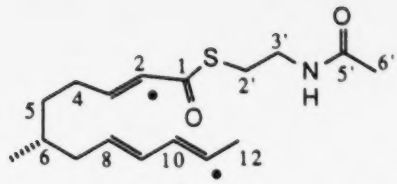
Condensation Reaction Using 8-[2-^{13}C]-Acetyloxymethyl-1-naphthyl Malonate (42a). A solution of **42a** (0.104 g, 0.344 mmol) in dry THF (5 mL) was slowly added to a solution of LHMDS (0.115 g, 0.688 mmol) in dry THF (20 mL) at room

temperature. After stirring for 1.5 h, the reaction mixture was poured into 1N HCl (4 mL) and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (10 mL) and the combined Et_2O fractions were washed with H_2O (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The orange residue was purified by flash chromatography (SiO_2; 30% EtOAc in hexane + 1% formic acid) to give 8-hydroxy-1-naphthalenemethyl [2-^{13}C]-acetate (**30a**) (22.0 mg, 25%, *Rf* 0.58); 8-hydroxy-1-naphthalenemethyl [2,4-$^{13}C_2$]-acetoacetate (**31b**) (5.90 mg, 7%, *Rf* 0.51) which was partially unlabeled at C-2 methylene (5%) and C-4 methyl (3%); and unreacted starting material **42a** (20.6 mg, 23%, *Rf* 0.28). The products **30a** and **42a** had physical and spectral properties in good agreement with those previously quoted.

Data for **31b:** IR ($CHCl_3$ cast) 3600-3100 (br m), 1732 (s), 1704 (s), 1280 (s), 1157 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd, 1H, *J* = 7.8, 1.7 Hz), 7.50-7.28 (m, 3H), 7.23 (dd, 1H, *J* = 8.0, 7.7 Hz), 6.88 (dd, 1H, *J* = 7.3, 1.3 Hz), 6.20 (br s, 1H, OH), 5.84 (s, 2H, OC$\underline{H}_2$), 3.55 (d, 1.9H, *J* = 130.3 Hz, ^{13}C$\underline{H}_2$), 3.55 (s, 0.1H, ^{12}C$\underline{H}_2$), 2.26 (dd, 2.9H, *J* = 128.2, 1.5 Hz, ^{13}C$\underline{H}_3$), 2.26 (d, 0.1H, *J* = 1.5 Hz, ^{12}C$\underline{H}_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.91 (d, *J* = 67.4 Hz, O$\underline{C}$(O)^{13}CH$_2$), 152.68 (C-1), 136.39 (Ar-$\underline{C}$), 130.70 (Ar-$\underline{C}$), 129.55 ($\underline{C}$H), 128.22 ($\underline{C}$H), 126.19 ($\underline{C}$H), 125.62 ($\underline{C}$H), 123.26 (Ar-$\underline{C}$), 121.95 ($\underline{C}$H), 112.43 ($\underline{C}$H), 68.71 (O$\underline{C}$H$_2$), 50.24 (d, *J* = 14.8 Hz, $^{13}\underline{C}$H$_2$C(O)^{13}CH$_3$), 30.28 (d, *J* = 14.8 Hz, ^{13}CH$_2$C(O)$^{13}\underline{C}$H$_3$); MS (EI) calcd for $^{13}C_2{}^{12}C_{13}H_{14}O_4$ 260.0960, found 260.0959 (M$^+$, 3.4), 156.0575 (100).

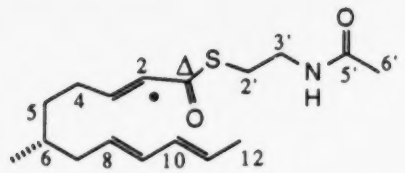


(6*R*)-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoic Acid *N*-Acetylcysteamine Thioester (50). A modification of the method used by Parker was followed.[105] A solution of the acid **85** (860 mg, 4.13 mmol) in dry CH_2Cl_2 (7 mL) was treated simultaneously with a solution of *N*-acetylcysteamine **86** (581 mg, 4.87 mmol) in CH_2Cl_2 (7 mL), and a solution of DCC (1.02 g, 4.95 mmol) and 4-dimethylaminopyridine (19.6 mg) in CH_2Cl_2 (7 mL) over 5 min at -15 °C. The resultant cloudy white solution was stirred overnight at room temperature. The mixture was concentrated *in vacuo* to afford a yellow oil, which was purified by flash chromatography (SiO_2; 40 x 120 mm, 100% EtOAc, R_f 0.33) to yield **50** (970 mg, 76%) as a white solid: mp 38-39 °C; $[\alpha]_D^{20}$ -7.41° (*c* 0.081, CH_2Cl_2); IR (CH_2Cl_2 cast) 3321 (br s), 3085 (m), 3080 (m), 2944 (s), 2927 (s), 2870 (s), 2850 (s), 1657 (s), 1626 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, 1H, *J* = 15.5, 7.4 Hz, H-3), 6.11 (dt, 1H, *J* = 15.5, 1.5 Hz, H-2), 6.01 (ddq, 1H, *J* = 14.2, 10.2, 1.5 Hz, H-10), 5.95 (ddt, 1H, *J* = 14.2, 10.2, 1.2 Hz, H-9), 5.57 (dq, 1H, *J* = 14.2, 6.6 Hz, H-11), 5.91-5.83 (br s, 1H, H-4'), 5.48 (dt, 1H, *J* = 14.2, 7.2 Hz, H-8), 3.44 (dt, 2H, *J* = 6.3, 5.9 Hz, H-3'), 3.07 (t, 2H, *J* = 6.3 Hz, H-2'), 2.31-2.12 (m, 2H, H-4), 2.06 (ddd, *J* = 13.7, 7.2, 6.1 Hz, 1 x H-7), 1.94 (ddd, *J* = 13.7, 7.4, 7.2 Hz, 1 x H-7), 1.95 (s, 3H, H-6'), 1.72 (d, 3H, *J* = 6.6 Hz, H-12), 1.55-1.45 (m, 2H, 1 x H-5 & H-6), 1.30-1.25 (m, 1H, 1 x H-5), 0.87 (d, 3H, *J* = 6.6 Hz, 6-$C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.36 (C-1), 170.34 (C-5'), 146.77 (C-3), 131.97 (C-9), 131.55 (C-10), 129.66 (C-8), 128.27 (C-2), 127.20 (C-11), 39.86 (C-7), 39.84 (C-3'), 34.55 (C-4), 32.87 (C-6), 29.92 (C-5), 28.26 (C-2'), 23.20 (C-6'), 19.32 (6-$\underline{C}H_3$), 17.99 (C-12); MS (CI, NH_3) 327 (MNH_4^+, 8), 310 (MH^+, 14); Anal. Calcd for $C_{17}H_{26}NO_2S$: C, 65.98; H, 8.79. Found: C, 66.24; H, 9.03.



• = ^{13}C

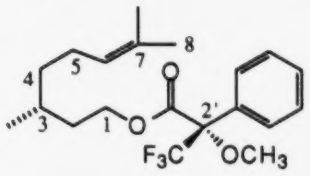
(6*R*)-[2,11-$^{13}C_2$]-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoic Acid *N*-Acetylcysteamine Thioester (50a). The same method as for the preparation of NAC thioester **50** was employed. Thus, coupling of labeled triene acid **85a** (599 mg, 2.85 mmol) with *N*-acetylcysteamine (**86**) (0.705 g, 3.42 mmol) afforded **50a** (544 mg, 61%): mp 38.5-39.5 °C; $[\alpha]_D^{20}$ -10.3° (*c* 0.087, CH_2Cl_2); IR (CH_2Cl_2 cast) 3400-3100 (br m), 3100-3000 (br w), 2955 (m), 2926 (m), 1656 (s), 1608 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.92 (dtd, 1H, *J* = 15.6, 7.0, 1.0 Hz, H-3), 6.12 (ddt, 1H, *J* = 161.0, 15.6, 1.5 Hz, H-2), 6.05–5.85 (m, 2H, H-9 & H-10), 5.57 (ddq, 1H, *J* = 150.2, 14.2, 6.7 Hz, H-11), 5.91-5.83 (br s, 1H, H-4'), 5.48 (dt, 1H, *J* = 14.2, 7.2 Hz, H-8), 3.45 (dt, 2H, *J* = 6.1, 6.0 Hz, H-3'), 3.08 (t, 2H, *J* = 6.1 Hz, H-2'), 2.31-2.12 (m, 2H, H-4), 2.05 (ddd, *J* = 13.7, 7.2, 6.1 Hz, 1 x H-7), 1.94 (ddd, *J* = 13.7, 7.4, 7.2 Hz, 1 x H-7), 1.96 (s, 3H, H-6'), 1.73 (dd, 3H, *J* = 6.7, 6.7 Hz, H-12), 1.60-1.40 (m, 2H, 1 x H-5 & H-6), 1.35-1.20 (m, 1H, 1 x H-5), 0.88 (d, 3H, *J* = 6.5 Hz, 6-C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.30 (d, *J* = 76.0 Hz, C-1), 170.27 (C-5'), 146.72 (d, *J* = 70.0 Hz, C-3), 131.97 (C-9), 131.66 (d, *J* = 72.5 Hz, C-10), 129.66 (C-8), 128.30 (C-2), 127.20 (C-11), 39.79 (C-7), 39.72 (C-3'), 34.50 (d, *J* = 3.5 Hz, C-4), 32.88 (C-6), 29.92 (C-5), 28.29 (C-2'), 23.18 (C-6'), 19.32 (6-<u>C</u>H$_3$), 17.96 (d, *J* = 44.3 Hz, C-12); **MS** (CI, NH_3) 329 (MNH_4^+, 25), 312 (MH^+, 100); Anal. Calcd for $^{13}C_2{}^{12}C_{15}H_{26}NO_2S$: C, 66.20; H, 8.74. Found: C, 66.00; H, 9.08.



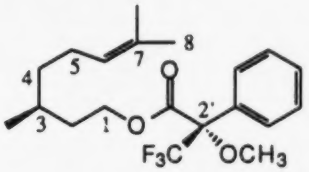
• = ^{13}C

Δ = $^{13/14}C$

30:70 Mixture of [1,2-$^{13}C_2$, 1-^{14}C] : [2-^{13}C, 1-^{14}C]-(6*R*)-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoic Acid *N*-Acetylcysteamine Thioester (50b). The same method as for the preparation of NAC ester **50** was employed. Thus, coupling of ^{14}C-labeled triene acid **85b** (410 mg, 1.94 mmol) with *N*-acetylcysteamine (**86**) (0.273 g, 2.29 mmol) afforded **50b** (310 mg, 51%) still containing the 2*E*,8*E*,10*Z*-isomer (11% by ^1H NMR integration): 22.3 μCi/mmol; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98–6.86 (m, 1H, H-3), 6.12 (ddm, 1H, *J* = 161.0, 15.6 Hz, H-2), 6.05–5.85 (m, 2H, H-9 & H-10), 5.57 (dq, 1H, *J* = 14.2, 6.5 Hz, H-11), 5.91-5.83 (br s, 1H, H-4'), 5.48 (dt, 1H, *J* = 14.2, 7.2 Hz, H-8), 3.45 (dt, 2H, *J* = 6.3, 6.0 Hz, H-3'), 3.08 (t, 2H, *J* = 6.3 Hz, H-2'), 2.30-2.10 (m, 2H, H-4), 2.10-1.85 (m, 2H, H-7), 1.96 (s, 3H, H-6'), 1.75 (d, 3H, *J* = 6.7 Hz, H-12), 1.60-1.40 (m, 2H, 1 x H-5 & H-6), 1.35-1.20 (m, 1H, 1 x H-5), 0.89 (d, 3H, *J* = 6.5 Hz, 6-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.44 (d, *J* = 62.0 Hz, C-1), 170.31 (C-5'), 146.71 (d, *J* = 70.0 Hz, C-3), 131.98 (C-9), 131.66 (C-10), 129.63 (C-8), 128.23 (d & s, *J* = 62.0 Hz, C-2), 127.13 (C-11), 39.72 (C-7), 39.65 (C-3'), 34.43 (d, *J* = 3.0 Hz, C-4), 32.81 (C-6), 29.90 (C-5), 28.22 (C-2'), 23.11 (C-6'), 19.24 (6-$\underline{C}H_3$), 17.90 (C-12).

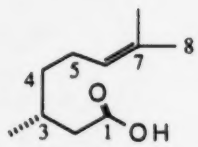


(*R*)-Citronellyl (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetate (53). The same procedure as for the preparation of diastereomer **54** was used. Thus, reaction of (*R*)-citronellol (0.405 mL, 2.22 mmol) with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (748 mg, 2.96 mmol) afforded **53** (764 mg, 92%) having spectral data similar to **54**, except; $[\alpha]_D^{20}$ +42.0° (*c* 0.21, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 4.48-4.28 (m, 2H, $C\underline{H}_2OCO$); Anal. Calcd for $C_{20}H_{27}F_3O_3$: C, 64.50; H, 7.31. Found: C, 64.25; H, 7.19.

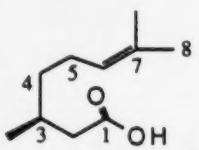


(*S*)-Citronellyl (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetate (54). A modification of the procedure of Dale *et al.* was adopted.[82] (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (748 mg, 2.96 mmol) was added to a mixture of (*S*)-citronellol (0.450 mL, 2.47 mmol) and distilled pyridine (1.0 mL) in dry CCl_4 (1.5 mL). After stirring at room temperature for 18 h, the ixture was treated with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL), and the combined organic layers were washed with 1N HCl (4 x 50 mL), saturated Na_2CO_3 (50 mL), and H_2O (50 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield **54** (873 mg, 95%) as a clear oil: $[\alpha]_D^{20}$ +37.4° (*c* 0.13, $CHCl_3$); IR ($CHCl_3$ cast) 2989 (s), 2920 (s), 1749 (s), 1185, (s), 1170 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.59-7.47 (m, 2H, Ar-H), 7.44-7.38 (m, 3H, Ar-H), 5.05 (br t, 1H, *J* = 7.1 Hz, H-6), 4.37 (dd, 2H, *J* = 7.1, 6.3 Hz, H-1), 3.56 (d, 3H, *J* = 2.0 Hz, $OC\underline{H}_3$), 2.07-1.85 (m,

2H, H-5), 1.66 (s, 3 H, CH=CHC<u>H</u>$_3$), 1.57 (s, 3H, CH=CHC<u>H</u>$_3$), 1.58-1.50 (m, 1H, H-3), 1.48-1.38 (m, 1H, 1 x H-2), 1.38-1.29 (m, 1H, 1 x H-4), 1.28-1.12 (m, 1H, 1 x H-4), 0.90 (d, 3H, J = 6.6 Hz, 3-C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.59 (C-1'), 132.52 (*ipso*-C), 131.42 (C-7), 129.54 (<u>C</u>H), 128.37 (<u>C</u>H), 127.38 (<u>C</u>H), 124.41 (C-6), 123.41 (q, J = 288 Hz, <u>C</u>F$_3$), 84.69 (d, J = 27.17 Hz, C-2'), 64.90 (C-1), 55.34 (O<u>C</u>H$_3$), 36.86 (<u>C</u>H$_2$), 35.31 (<u>C</u>H$_2$), 29.30 (C-3), 25.61 (C-8), 25.35 (C-4), 19.16 (3-<u>C</u>H$_3$), 17.57 (7-<u>C</u>H$_3$); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -71.8 (s, 3F, C<u>F</u>$_3$); MS (CI, NH_3) 390 (MNH_4^+, 100), 373 (MH^+, 3.7); Anal. Calcd for $C_{20}H_{27}F_3O_3$: C, 64.50; H, 7.31. Found: C, 64.63; H, 7.33.

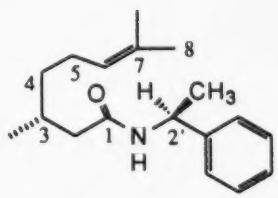


(*R*)-Citronellic Acid (55). The same procedure as for the preparation of acid **56** was used. Thus, oxidation of (*R*)-citronellol (0.310 mL, 1.98 mmol) with pyridinium dichromate (2.30 g, 6.11 mmol) afforded **55** (87.5 mg, 37%) having physical and spectral data similar to **56**.

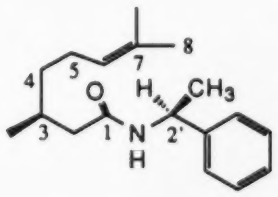


(*S*)-Citronellic Acid (56). The method of Corey and Schmidt was followed.[83] A solution of pyridinium dichromate (2.30 g, 6.11 mmol) in dry DMF (5 mL) was added dropwise (20 min) to a solution of (*S*)-citronellol (0.317 g, 2.03 mmol) in DMF (2 mL). After stirring overnight at room temperature, the mixture was diluted with Et_2O (15 mL) and filtered through $MgSO_4$. The filtrate was washed with H_2O (5 mL) and dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography

(SiO_2; 60% Et_2O in pentane, R_f 0.49) to afford **56** (0.129 g, 38%): IR ($CHCl_3$ cast) 3400-2500 (br), 2964 (s), 2924 (s), 1709 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.36 (br s, 1H, COO<u>H</u>), 5.08 (tm, 1H, *J* = 7.1 Hz, H-6), 2.38 (dd, 1H, *J* = 15.0, 5.6 Hz, 1 x H-2), 2.15 (dd, 1H, *J* = 15.0, 6.8 Hz, 1 x H-2), 2.08-1.90 (m, 3H, H-3 & H-5), 1.69 (s, 3 H, CH=CHC<u>H</u>$_3$), 1.60 (s, 3H, CH=CHC<u>H</u>$_3$), 1.48-1.16 (m, 2H, H-4), 0.98 (d, 3H, *J* = 6.8 Hz, 3-C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.93 (C-1), 131.65 (C-6), 124.24 (C-7), 41.60 (C-2), 36.77 (C-5), 29.88 (C-3), 25.69 (C-8), 25.46 (C-4), 19.62 (3-<u>C</u>H$_3$), 17.64 (7-<u>C</u>H$_3$); MS (CI, NH_3) 188 (MNH_4^+, 100), 171 (MH^+, 23).

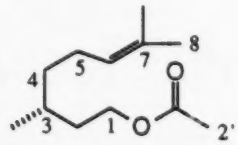


***N*-(1*S*)-Phenylethyl (*R*)-Citronellamide (57).** The same procedure as for the preparation of diastereomer **58** was used. Thus, amidation of (*R*)-citronellic acid (**55**) (0.117 mL, 0.685 mmol) with (*S*)-(-)-1-phenylethylamine (0.145 mL, 1.12 mmol) afforded the crude amide. A portion of this material (100 mg) was purified by flash chromatography (SiO_2; 50% Et_2O in pentane, R_f 0.21) to yield **57** (70.1 mg, 70%) having physical and spectral data similar to **58**, except; mp 56-57 °C; $[\alpha]_D^{20}$ -60.5° (*c* 0.16, $CHCl_3$); Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95. Found: C, 78.93; H, 10.02.



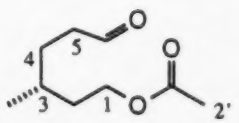
***N*-(1*S*)-Phenylethyl (*S*)-Citronellamide (58).** The procedure of Huffer ans Schreirer was used.[84] Dicyclohexylcarbodiimide (DCC, 0.148 g, 7.17 mmol) and (*S*)-(-)-

1-phenylethylamine (0.148 mL, 1.14 mmol) were added to (*S*)-citronellic acid **56** (0.119 g, 6.98 mmol) in dry $CHCl_3$ (2mL) and the mixture was heated to 50 °C for 20 min. After cooling, the mixture was filtered, and the solvent was removed *in vacuo* from the filtrate to yield a residue that could be used without further purification. A portion of this material (100 mg) was purified by flash chromatography (SiO_2; 50% Et_2O in pentane, *Rf* 0.21) to yield **58** (71.4 mg, 71%) as a white solid: mp 60-61 °C; $[\alpha]_D^{20}$ -58.4° (*c* 0.41, $CHCl_3$); IR ($CHCl_3$ cast) 3280 (br s), 3065 (w), 3035 (w), 2970 (s), 2930 (s), 1638 (s), 1544 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 3H, Ar-H), 7.28-7.22 (m, 2H, Ar-H), 5.68 (br d, 1H, *J* = 6.3 Hz, H-1'), 5.16 (dq, 1H, *J* = 7.0, 6.9 Hz, H-2'), 5.08 (br t, 1H, *J* = 7.1 Hz, H-6), 2.20 (dd, 1H, *J* = 13.0, 5.0 Hz, 1 x H-2), 2.07-1.88 (m, 4H, 1 x H-2 & H-3 & H-5), 1.67 (s, 3 H, CH=CHC$\underline{H}_3$), 1.59 (s, 3H, CH=CHC$\underline{H}_3$), 1.49 (d, 3H, *J* = 6.9 Hz, 2'-C$\underline{H}_3$), 1.41-1.32 (m, 1H, 1 x H-4), 1.24-1.14 (m, 1H, 1 x H-4), 0.91 (d, 3H, *J* = 6.3 Hz, 3-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.57 (C-1), 143.33 (*ipso*-C), 131.53 (C-6), 128.69 (C$\underline{H}$), 127.36 (C$\underline{H}$), 126.25 (C$\underline{H}$), 124.38 (C-7), 48.58 (C-2'), 44.67 (C-2), 36.91 (C-5), 30.56 (C-3), 25.73 (C-8), 25.48 (C-4), 21.67 (2'-C$\underline{H}_3$), 19.57 (3-C$\underline{H}_3$), 17.69 (7-C$\underline{H}_3$); MS (EI) calcd for $C_{18}H_{27}NO$ 273.2093, found 273.2091 (M^+, 49), 258.1855 (1.7); Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95. Found: C, 79.09; H, 10.09.



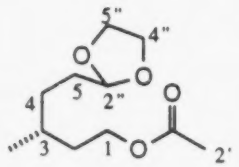
(*R*)-Citronellyl Acetate (60).[86] An ice-cooled (0 °C) stirred solution of (*R*)-citronellol (21.9 g, 140 mmol) in dry THF (600 mL) was treated with freshly distilled acetyl chloride (13.6 mL, 192 mmol). After 5 min, distilled triethylamine (29.0 mL, 208 mmol) was added dropwise over a period of 1 h to the cooled solution. The reaction mixture was then stirred at room temperature for 1.5 h. The solvent was removed *in vacuo*

and flash chromatography (SiO_2; 5% EtOAc in hexane, R_f 0.32) of the mixture yielded a clear colorless oil **60** (26.5 g, 95%): bp 97-98 °C (3.5 mm Hg); $[\alpha]_D^{20}$ +3.20° (*c* 2.91, $CHCl_3$) (lit.[86] $[\alpha]_D^{20}$ +5.12° (*c* 5.86, $CHCl_3$)); IR (CH_2Cl_2 cast) 2966 (s), 2924 (s), 2918 (s), 2873(m), 2859, (m), 1743 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (tm, 1H, *J* = 7.0 Hz, H-6), 4.15-4.05 (m, 2H, H-1), 2.03 (s, 3H, H-2'), 2.05-1.92 (m, 2H, H-5), 1.70-1.58 (m, 1H, 1 x H-2), 1.67 (s, 3H, HC=CC$\underline{H}_3$), 1.59 (s, 3H, HC=CC$\underline{H}_3$), 1.58-1.50 (m, 1H, H-3), 1.48-1.38 (m, 1H, 1 x H-2), 1.38-1.29 (m, 1H, 1 x H-4), 1.28-1.12 (m, 1H, 1 x H-4), 0.90 (d, 3H, *J* = 6.6 Hz, 3-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.21 (C-1'), 131.34 (C-7), 124.61 (C-6), 63.04 (C-1), 36.99 ($\underline{C}H_2$), 35.45 ($\underline{C}H_2$), 29.50 (C-3), 25.71 (C-8), 25.40 (C-4), 21.04 (C-2'), 19.43 (3-$\underline{C}H_3$), 17.65 (7-$\underline{C}H_3$); MS (CI, NH_3) 216 (MNH_4^+, 100), 199 (MH^+, 12); Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.67; H, 11.19. Found: C, 72.65; H, 11.45.

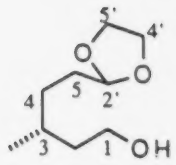


(3*R*)-Methyl-6-oxohexyl Acetate (61). The procedure of Clive *et al.* was used.[87] Ozonized oxygen, cooled by passage through a glass coil immersed in a cold-bath at -78 °C, was bubbled into a cold (-78 °C) solution of **60** (6.17 g, 31.11 mmol) in dry CH_2Cl_2 (60 mL) until the solution had acquired a blue tint (1.5 h). Triphenylphosphine (8.98 g, 34.2 mmol) was added and the reaction mixture was stirred at -78 °C for a further 30 min. The cooling bath was then removed and stirring was continued for 2 h. The solution was evaporated *in vacuo* and the residue was purified by flash chromatography (SiO_2; 30% Et_2O in pentane, R_f 0.25) to yield **61** (4.56 g, 85%) as a colourless volatile oil: $[\alpha]_D^{20}$ +1.87° (*c* 7.18, $CHCl_3$); IR ($CHCl_3$ cast) 2980 (m), 2930 (m), 2720 (w), 1740 (s), 1725 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (br s, 1H, H-6), 4.12-4.01 (m, 2H, H-1), 2.50-2.35 (m, 2H, H-5), 2.00 (s, 3H, H-2'), 1.71-1.57 (m, 2H, H-2), 1.60-

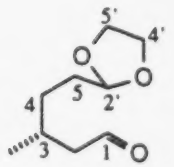
1.50 (m, 1H, H-3), 1.49-1.40 (m, 2H, H-4), 0.89 (d, 3H, J = 6.4 Hz, 3-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.34 (C-6), 171.09 (C-1'), 62.53 (C-1), 41.44 (C-5), 35.19 ($\underline{C}H_2$), 29.43 (C-3), 28.69 ($\underline{C}H_2$), 20.59 (C-2'), 19.08 (3-$\underline{C}H_3$); MS (CI, NH_3) 190 (MNH_4^+, 100), 173 (MH^+, 4.2); Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.72; H, 9.59.



(3*R*)-5-(2-Dioxolanyl)-3-methylpentyl Acetate (62). A modification of the procedure of Daignault and Eliel was used.[88] A mixture of aldehyde **61** (4.06 g, 23.6 mmol), distilled ethylene glycol (1.87 g, 30.2 mmol), and *p*-toluenesulfonic acid monohydrate (481 mg, 2.53 mmol) in dry benzene (100 mL) was heated to reflux for 5 h using a soxhlet containing CaH_2. The solution was cooled, diluted with Et_2O (200 mL), washed with saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (1 x 50 mL), and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatograghy (SiO_2, 67% Et_2O in pentane, R_f 0.36) to give **62** (3.34 g, 85%) as a clear oil: $[\alpha]_D^{20}$ +2.97° (*c* 5.38, $CHCl_3$); IR ($CHCl_3$ cast) 2956 (m), 1740 (s), 1242 (m), 1049 (m), 1036 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.82 (t, 1H, J = 4.6 Hz, H-2"), 4.08 (br t, 2H, J = 7.0 Hz, H-1), 4.01-3.88 (m, 2H, 1 x H-4" & 1 x H-5"), 3.88-3.77 (m, 2H, 1 x H-4" & 1 x H-5"), 2.02 (s, 3H, H-2'), 1.80-1.20 (m, 7H, H-2 & H-3 & H-4 & H-5), 0.90 (d, 3H, J = 6.6 Hz, 3-C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.64 (C-1'), 104.39 (C-2"), 64.54 (C-4" & C-5"), 62.48 (C-1), 35.13 ($\underline{C}H_2$), 31.02 ($\underline{C}H_2$), 30.56 ($\underline{C}H_2$), 29.59 (C-3), 20.59 (C-2'), 19.06 (3-$\underline{C}H_3$); MS (CI, NH_3) 234 (MNH_4^+, 100), 217 (MH^+, 25); Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.93; H, 9.63.

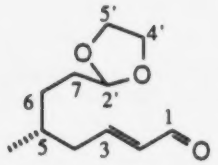


(3*R*)-5-(2-Dioxolanyl)-3-methylpentanol (63). Sodium methoxide (88.7 mg, 1.63 mmol) was added to a solution of the acetate **62** (4.09 g, 18.9 mmol) in dry MeOH (90 mL). After stirring at room temperature overnight, the solvent volume was reduced *in vacuo*, and the mixture was diluted with Et_2O (300 mL), washed with H_2O (2 x 50 mL), and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* and purification of the residue by flash chromatograghy (SiO_2; 100% Et_2O, R_f 0.36) gave **63** (2.72 g, 83%) as a clear oil: $[\alpha]_D^{20}$ +4.72° (*c* 2.54, $CHCl_3$); IR ($CHCl_3$ cast) 3429 (br s), 2953 (s), 2928 (s), 2875 (s), 1142 (s), 1012 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (t, 1H, *J* = 4.7 Hz, H-2'), 4.00-3.88 (m, 2H, 1 x H-4' & 1 x H-5'), 3.88-3.77 (m, 2H, 1 x H-4' & 1 x H-5'), 3.75-3.60 (m, 2H, H-1), 1.79 (br s, 1H, O<u>H</u>), 1.75-1.53 (m, 4H, 1 x H-2 & H-3 & H-5), 1.52-1.33 (m, 2H, 1 x H-2 & 1 x H-4), 1.32-1.20 (m, 1H, 1 x H-4), 0.90 (d, 3H, *J* = 6.4 Hz, 3-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.87 (C-2'), 64.86 (C-4' & C-5'), 61.00 (C-1), 39.73 (C-5), 31.31 (<u>C</u>H_2), 30.93 (<u>C</u>H_2), 29.37 (C-3), 19.53 (3-<u>C</u>H_3); MS (CI, NH_3) 192 (MNH_4^+, 8), 175 (MH^+, 1.9), 73 (100); Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.13; H, 10.68.

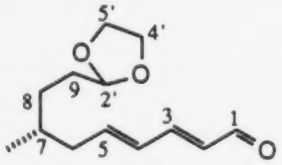


(3*R*)-5-(2-Dioxolanyl)-3-methylpentanal (64). The procedure of Swern and coworkers was used.[89] Dry DMSO (2.11 mL, 29.8 mmol) was added dropwise over 5 min to a stirred cooled (-78 °C) solution of distilled oxalyl chloride (1.36 mL, 15.6 mmol) in CH_2Cl_2 (30 mL). After 10 min, a solution of the alcohol **63** (2.72 g,

15.6 mmol) in CH_2Cl_2 (15 mL) was added over 30 min. The resultant slurry was stirred for 20 min at -78 °C and then dry triethylamine (7.43 mL, 53.3 mmol) was injected dropwise over 30 min. Stirring was continued at -78°C for 20 min, the cold bath removed, and after a further 30 min, H_2O (10 mL) was added. The mixture was stirred for a further 10 min and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with 10% v/v aqueous HCl (2 x 7 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), and brine (1 x 10 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by flash chromatograghy (SiO_2; 50% Et_2O in pentane, R_f 0.32) to give **64** (2.15 g, 80%) as a clear oil: $[\alpha]_D^{20}$ +14.2° (*c* 3.56, $CHCl_3$); IR (neat) 2954 (s), 2930 (s), 2879 (s), 2720 (m), 1724 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (br s, 1H, H-1), 4.70 (t, 1H, *J* = 4.7 Hz, H-2'), 3.86-3.77 (m, 2H, 1 x H-4' & 1 x H-5'), 3.77-3.67 (m, 2H, 1 x H-4' & 1 x H-5'), 2.29 (ddd, 1H, *J* = 16.3, 5.5, 1.0 Hz, 1 x H-2), 2.12 (ddd, 1H, *J* = 16.3, 7.9, 2.0 Hz, 1 x H-2), 2.03-1.90 (m, 1H, H-3), 1.63-1.47 (m, 2H, H-5), 1.28-1.18 (m, 2H, H-4), 0.84 (d, 3H, *J* = 6.6 Hz, 3-$\underline{C}H_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.21 (C-1), 104.20 (C-2'), 64.62 (C-4' & C-5'), 50.66 (C-2), 31.07 ($\underline{C}H_2$), 30.63 ($\underline{C}H_2$), 27.73 (C-3), 19.56 (3-$\underline{C}H_3$); MS (CI, NH_3) 190 (MNH_4^+, 3.8), 173 (MH^+, 1.7); Anal. Calcd for $C_9H_{16}O_3$: C, 62.75; H, 9.37. Found: C, 62.64; H, 9.53.



66



67

(5*R*)-*E*-7-(2-dioxolanyl)-5-methylhept-2-enal (66). A modification of the procedure of Brimacombe *et al.* was used.[90] A solution of aldehyde **64** (1.21 g, 7.03 mmol) and commercially available triphenylphosphoranylidene acetaldehyde (**65**) (2.32 g, 7.61 mmol) in dry benzene (60 mL) was heated to reflux at 85 °C for 15.5 h. The mixture was cooled to room temperature and solvent was removed *in vacuo* to leave a red

semi-solid residue. The mixture was triturated twice with Et_2O and the resultant red slurry was purified by reverse phase MPLC (RP-8; 30 x 280 mm, 58% MeOH in H_2O). The combined product containing fractions were partially evaporated *in vacuo* to remove MeOH, and the resultant aqueous mixture was extracted with Et_2O. The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*, to afford the desired product **66** (0.305 g, 22%, R_f 0.28). Similar treatment of the other fractions gave (7*R*)-*E*,*E*-9-(2-dioxolanyl)-7-methylnona-2,4-dienal (**67**) (0.130 g, 9%, R_f 0.14), and unreacted aldehyde **64** (0.166 g, 12%).

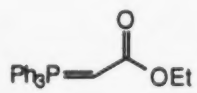
Data for aldehyde **66:** $[\alpha]_D^{20}$ +1.37° (*c* 2.56, $CHCl_3$); IR (CH_2Cl_2 cast) 2955 (m), 2878 (m), 1740 (w), 1692 (s), 1144 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.43 (d, 1H, *J* = 7.9 Hz, H-1), 6.77 (dt, 1H, *J* = 15.6, 7.5 Hz, H-3), 6.04 (ddt, 1H, *J* = 15.6, 7.9, 1.2 Hz, H-2), 4.80 (t, 1H, *J* = 4.6 Hz, H-2'), 3.95-3.82 (m, 2H, 1 x H-4' & 1 x H-5'), 3.82-3.73 (m, 2H, 1 x H-4' & 1 x H-5'), 2.32 (ddd, 2H, *J* = 13.8, 7.5, 6.5 Hz, 1 x H-4), 2.15 (ddd, 2H, *J* = 13.8, 7.5, 6.5 Hz, 1 x H-4), 1.75-1.54 (m, 3H, H-5 & H-7), 1.50-1.39 (m, 1H, 1 x H-6), 1.34-1.21 (m, 1H, 1 x H-6), 0.92 (d, 3H, *J* = 6.6 Hz, 5-$C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.01 (C-1), 157.41 (C-3), 134.22 (C-2), 104.42 (C-2'), 64.83 (C-4' & C-5'), 40.01 (C-4), 32.39 (C-5), 31.30 ($\underline{C}H_2$), 30.56 ($\underline{C}H_2$), 19.38 (5-$\underline{C}H_3$); MS (CI, NH_3) 216 (MNH_4^+, 100), 199 (MH^+, 44); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.16. Found: C, 66.76; H, 9.37.

Data for the dienal **67:** IR (CH_2Cl_2 cast) 2955 (m), 2878 (m), 1740 (w), 1689 (s), 1140 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.54 (d, 1H, *J* = 8.0 Hz, H-1), 7.09 (dd, 1H, *J* = 15.2, 10.0 Hz, H-3), 6.28 (m, 2H, H-4 & H-5), 6.07 (dd, 1H, *J* = 15.2, 8.0 Hz, H-2), 4.83 (t, 1H, *J* = 4.6 Hz, H-2'), 3.95-3.82 (m, 2H, 1 x H-4' & 1 x H-5'), 3.82-3.73 (m, 2H, 1 x H-4' & 1 x H-5'), 2.31-2.03 (m, 2H, H-6), 1.80-1.60 (m, 3H, H-7 & H-9), 1.60-1.25 (m, 2H, H-8), 0.92 (d, 3H, *J* = 6.6 Hz, 7-$C\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.83 (C-1), 152.51 (C-3), 145.56 (C-5), 130.13 (C-4), 129.98 (C-2), 104.59 (C-2'), 64.85 (C-4' & C-5'), 40.52 (C-6), 32.88 (C-7), 31.44 ($\underline{C}H_2$), 30.60 ($\underline{C}H_2$), 19.43

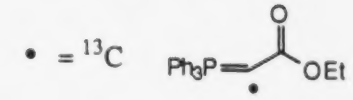
(7-$\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1412 (M^+, 1.2).

Procedure B. The procedure for the formation of aldehyde **64** was used. Thus, oxidation of alcohol **71** (3.64 g, 18.2 mmol) with DMSO (2.46 mL, 34.6 mmol) and oxalyl chloride (1.58 mL, 18.2 mmol) afforded **66** (3.18 g, 88%) as an oil, with physical and spectra properties in good agreement with those given in the previous preparation above.

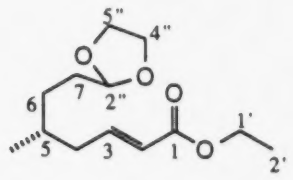
If a mixture of *Z*- and *E*-isomers of the alcohol was used during the oxidation, a mixture of *Z*- and *E*-aldehydes was produced. The mixture was difficult to separate. Spectral data for the *Z*-isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.91 (d, 1H, *J* = 8.0 Hz, H-1), 6.48 (dt, 1H, *J* = 11.6, 8.1 Hz, H-3), 5.84 (ddt, 1H, *J* = 11.6, 8.0, 1.6 Hz, H-2), 4.67 (t, 1H, *J* = 4.6 Hz, H-2'), 3.95-3.83 (m, 2H, 1 x H-4' & 1 x H-5'), 3.82-3.73 (m, 2H, 1 x H-4' & 1 x H-5'), 2.42-2.12 (m, 2H, H-4), 1.75-1.54 (m, 3H, H-5 & H-7), 1.50-1.39 (m, 1H, 1 x H-6), 1.34-1.21 (m, 1H, 1 x H-6), 0.82 (d, 3H, *J* = 6.6 Hz, 5-$\underline{C}H_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.26 (C-1), 156.53 (C-3), 130.90 (C-2), 104.22 (C-2'), 64.60 (C-4' & C-5'), 39.72 (C-4), 32.94 (C-5), 31.12 ($\underline{C}H_2$), 30.28 ($\underline{C}H_2$), 19.03 (5-$\underline{C}H_3$).



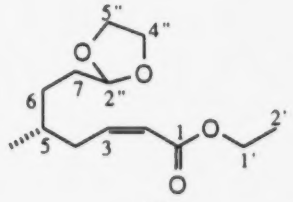
(Carbethoxymethylene)triphenylphosphorane (68). The method of Isler *et al.* was used.[91] A mixture of ethyl 2-bromoacetate (76.5 g, 458 mmol) and triphenylphosphine (138 g, 525 mmol) in toluene (500 mL) was heated at 120 °C for 1 h. The solvent was removed *in vacuo*, and the resulting solid was washed with hexane (200 mL). The residue was dissolved in H_2O (2 L) at 0 °C, and a solution of NaOH (22 g) in H_2O (250 mL) was added over 1 h. The mixture was stirred for 30 min, and then extracted with toluene (3 x 250 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to afford **68** (135 g, 85%). mp 128-130 °C (lit.[91] mp 128-130 °C); MS (EI) calcd for $C_{22}H_{21}O_2P$ 348.1279, found 348.1199 (M^+, 14).



[2-^{13}C]-(Carbethoxymethylene)triphenylphosphorane (68a). The same method as for the preparation of unlabeled Wittig reagent **68** was employed. Thus, reaction of ethyl [2-^{13}C]-bromoacetate (1.87 g, 11.2 mmol) (isotopic purity 99% ^{13}C) with triphenylphosphine (3.59 g, 13.7 mmol) after base treatment afforded **68a** (3.81 g, 98%): mp 127-129 °C; MS (EI) calcd for $^{13}C^{12}C_{21}H_{21}O_2P$ 349.1313, found 349.1297 (M^+, 22).



69



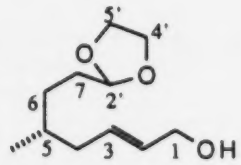
70

Ethyl (5*R*)-*E*-7-(2-dioxolanyl)-5-methylhept-2-enoate (69) and its *Z*-isomer 70. The method of Seebach and coworkers was used.[104] A solution of aldehyde **64** (1.21g, 7.03 mmol) and (carbethoxymethylene)triphenylphosphorane (**68**) (2.65 g, 7.61 mmol) in dry benzene (60 mL) was heated to reflux at 85 °C for 9 h. The mixture was heated to reflux for a further 3 h; the solvent was removed *in vacuo* and a semi-solid pink residue was obtained. The residue was purified by flash chromatography (SiO_2; 40 x 215 mm, 25% Et_2O in pentane) to yield the minor *Z*-isomer **70** (0.114 g, 7%, R_f 0.31), and desired *E*-isomer **69** (1.50 g, 88%, R_f 0.26) as clear oils.

Data for the *E*-isomer **69**: $[\alpha]_D^{20}$ +3.77° (*c* = 5.25, $CHCl_3$); IR ($CHCl_3$ cast) 2980 (m), 2955 (m), 2928 (m), 2906 (m), 2878 (m), 1720 (s), 1654 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.93 (dt, 1H, *J* = 15.6, 7.5 Hz, H-3), 5.81 (dt, 1H, *J* = 15.6, 1.4 Hz, H-2), 4.83 (t, 1H, *J* = 4.6 Hz, H-2"), 4.18 (q, 2H, *J* = 7.2 Hz, H-1'), 4.10-3.90 (m, 2H, 1 x H-4" & 1 x H-5"), 3.90-3.75 (m, 2H, 1 x H-4" & 1 x H-5"), 2.23 (dddd,

1H, *J* = 14.1, 7.5, 7.2, 1.4 Hz, 1 x H-4), 2.06 (dddd, 1H, *J* = 14.1, 7.6, 7.5, 1.4 Hz, 1 x H-4), 1.78-1-57 (m, 4H, H-5 & 1 x H-6 & H-7), 1.52-1.40 (m, 1H, 1 x H-6), 1.28 (t, 3H, *J* = 7.2 Hz, H-2'), 0.92 (d, 3H, *J* = 6.6 Hz, 5-C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.45 (C-1), 147.55 (C-3), 122.74 (C-2), 104.73 (C-2"), 64.89 (C-4" & C-5"), 60.04 (C-1'), 39.57 (C-4), 32.51 (C-5), 31.52 ($\underline{C}H_2$), 30.75 ($\underline{C}H_2$), 19.43 (5-$\underline{C}H_3$), 14.27 (C-2'); MS (CI, NH_3) 260 (MNH_4^+, 51), 243 (MH^+, 88); Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.42; H, 9.16. Found: C, 64.76; H, 9.49.

Data for the *Z*-isomer **70:** IR (CH_2Cl_2 cast) 2954 (s), 2928 (s), 2875 (s), 1720 (s), 1643 (m), 1177 (s), 1036 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.23 (dt, 1H, *J* = 11.6, 7.6 Hz, H-3), 5.78 (dt, 1H, *J* = 11.6, 1.5 Hz, H-2), 4.83 (t, 1H, *J* = 4.6 Hz, H-2"), 4.15 (q, 2H, *J* = 7.2 Hz, H-1'), 4.10-3.90 (m, 2H, 1 x H-4" & 1 x H-5"), 3.90-3.78 (m, 2H, 1 x H-4" & 1 x H-5"), 2.68-2.50 (m, 2H, H-4), 1.78-1.55 (m, 3H, H-5 & H-7), 1.55-1.38 (m, 2H, H-6), 1.28 (t, 3H, *J* = 7.2 Hz, H-2'), 0.92 (d, 3H, *J* = 6.6 Hz, 5-C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.45 (C-1), 148.96 (C-3), 120.57 (C-2), 104.79 (C-2"), 64.85 (C-4" & C-5"), 59.74 (C-1'), 35.88 (C-4), 33.24 (C-5), 31.50 ($\underline{C}H_2$), 30.74 ($\underline{C}H_2$), 19.42 (5-$\underline{C}H_3$), 13.95 (C-2'); MS (CI, NH_3) 260 (MNH_4^+, 38), 243 (MH^+, 57); MS (EI) calcd for $C_{13}H_{22}O_4$ 242.1518, found 241.1440 (4.3), 197.1174 (17).



(5*R*)-*E*-7-(2-Dioxolanyl)-5-methylhept-2-enol (71). A modification of the method of Nicolaou *et al.* was used.[92] A solution of ester **69** (1.27 g, 5.24 mmol) in CH_2Cl_2 (13 mL) was treated with DIBAL (2.23 g, 15.7 mmol) in CH_2Cl_2 (9 mL) over 10 min at -78 °C. The reaction mixture was stirred for 2 h at -78 °C, and then for 30 min at -30 °C, at which point MeOH (2 mL) was added to quench the excess of DIBAL. The

mixture was diluted with Et_2O (300 mL) and the layers were separated. The Et_2O phase was washed with saturated aqueous potassium-sodium tartrate (4 x 100 mL), and brine (2 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a clear oil. The residue was purified by flash chromatography (SiO_2; 30 x 220 mm, 75% Et_2O in pentane, R_f 0.26) to yield **71** (0.941 g, 90%) as an oil: $[\alpha]_D^{20}$ +4.73° (*c* 4.50, $CHCl_3$); IR ($CHCl_3$ cast) 3430 (br), 2958 (s), 2873 (s), 1410 (w), 970 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.70-5.60 (m, 2H, H-2 & H-3), 4.82 (t, 1H, *J* = 4.7 Hz, H-2'), 4.07 (d, 2H, *J* = 4.0 Hz, H-1), 4.02-3.90 (m, 2H, 1 x H-4' & 1 x H-5'), 3.90-3.78 (m, 2H, 1 x H-4' & 1 x H-5'), 2.20 (br s, 1H, O<u>H</u>), , 2.15-1.80 (m, 2H, H-4), 1.75-1.57 (m, 3H, H-5 & H-7), 1.57-1.35 (m, 2H, 1x H-6 & 1 x H-7), 1.35-1.15 (m, 1H, 1x H-6), 0.89 (d, 3H, *J* = 6.5 Hz, 5-C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.13 & 130.50 (<u>C</u>H=<u>C</u>H), 104.73 (C-2'), 64.75 (C-4' & H-5'), 63.46 (C-1), 39.46 (C-4), 32.92 (C-5), 31.34 (<u>C</u>H_2), 30.38 (<u>C</u>H_2), 19.31 (5-<u>C</u>H_3); MS (CI, NH_3) 218 (MNH_4^+, 20), 201 (MH^+, 1.2); Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.95; H, 10.07. Found: C, 65.77; H, 10.23.

If a mixture of *Z*- and *E*-isomers of the ethyl ester was used during the reduction, a mixture of *Z*- and *E*-alcohols was produced. This mixture was difficult to separate. Spectral data for the *Z*-isomer: ^1H NMR (200 MHz, $CDCl_3$) δ 5.70-5.60 (m, 2H, H-2 & H-3), 4.82 (t, 1H, *J* = 4.7 Hz, H-2'), 4.16 (d, 2H, *J* = 6.1 Hz, H-1), 4.02-3.90 (m, 2H, 1 x H-4' & 1 x H-5'), 3.90-3.78 (m, 2H, 1 x H-4' & 1 x H-5'), 2.20 (br s, 1H O<u>H</u>), , 2.15-1.80 (m, 2H, H-4), 1.75-1.57 (m, 3H, H-5 & H-7), 1.57-1.35 (m, 2H, 1x H-6 & 1 x H-7), 1.35-1.15 (m, 1H, 1x H-6), 0.89 (d, 3H, *J* = 6.5 Hz, 5-C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 130.75 & 129.65 (<u>C</u>H=<u>C</u>H), 104.74 (C-2'), 64.75 (C-4' & H-5'), 58.32 (C-1), 39.46 (C-4), 32.74 (C-5), 31.23 (<u>C</u>H_2), 30.16 (<u>C</u>H_2), 19.31 (5-<u>C</u>H_3).

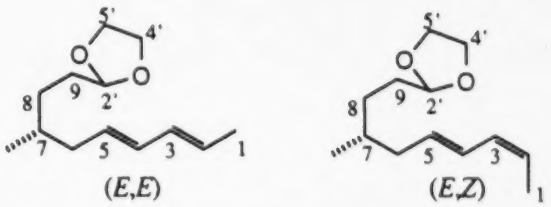
$$I^-$$
$$Ph_3P^+-CH_2CH_3$$

Ethyltriphenylphosphonium Iodide (72). A modification of the procedure of Barnhardt and McEwen was used.[97] A solution of triphenylphosphine (12.0 g, 45.8 mmol) in dry toluene (30 mL) was treated with distilled iodoethane (3.48 mL, 43.6 mmol) and the reaction mixture was heated to reflux for 1 h. The white slurry was cooled to room temperature and the crystalline material was collected by filtration to yield **72** (14.4 g, 79%), which was used without further purification: mp 158-160 °C (lit.[97] mp 164-165 °C); IR (KBr) 3081 (w), 3056 (w), 3050 (w), 2979 (w), 2886 (w), 2881 (m), 2798 (m) 1438 (s), 1115 (s) cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.95–7.84 (m, 6H, Ar-H), 7.84-7.70 (m, 9H, Ar-H), 3.54 (dq, 2H, J = 13.1, 7.4 Hz, $C\underline{H}_2CH_3$), 1.36 (dt, J = 19.8, 7.4 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, CD_3OD) δ 136.18 (d, J = 3.5 Hz, *para*-C),134.82 (d, J = 10.5 Hz, *meta*-C), 131.51 (d, J = 11.6 Hz, *ortho*-C), 119.55 (d, J = 86.5 Hz, *ipso*-C), 16.76 (d, J = 53.1 Hz, $\underline{C}H_2CH_3$), 7.05 (d, J = 5.0 Hz, $CH_2\underline{C}H_3$); MS (FAB; Cleland matrix) 417.12 (0.6).

$$I^-$$
$$Ph_3P^+-{}^{13}CH_2CH_3$$

[1-^{13}C]-Ethyltriphenylphosphonium Iodide (72a). The same procedure for as the formation of unlabeled **72** was used. Thus, reaction of [1-^{13}C]-iodoethane (3.00 g, 19.11 mmol) (isotopic purity 99% ^{13}C) with triphenylphosphine (5.28 g, 20.1 mmol) afforded **72a** (6.73 g, 84%): mp 158-159 °C; IR (KBr disk) 3081 (w), 3058 (w), 3050 (w), 2979 (w), 2886 (w), 2881 (m), 2799 (m) 1437 (s), 1113 (s) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.93–7.84 (m, 3H, Ar-H), 7.84-7.70 (m, 12H, Ar-H), 3.43 (ddq, 2H, J = 133.8, 13.1, 7.4 Hz, $C\underline{H}_2CH_3$), 1.36 (ddt, J = 19.8, 7.4, 4.4 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, CD_3OD) δ 136.34 (*para*-C),134.89 (d, J = 9.8 Hz, *meta*-C), 131.56 (d, J = 12.8 Hz, *ortho*-C), 119.70 (d, J = 88.7 Hz, *ipso*-C), 16.86 (d, J =

52.8 Hz, $^{13}\underline{C}H_2CH_3$), 7.04 (d, J = 27.7, 5.0 Hz, $^{13}CH_2\underline{C}H_3$); MS (FAB; Cleland matrix) 418.10 (1.9).

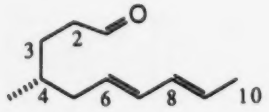


(7*R*)-*E*,*E*-9-(2-Dioxolanyl)-7-methylnona-2,4-diene (73). A modification of the method of Schlosser and Christmann was used.[93] The phosphonium salt **72** (0.295 g, 0.704 mmol) was suspended in dry THF (1.4 mL) and dry Et_2O (1.1 mL), and was stirred with phenyllithium (1.8 M in cyclohexane/Et_2O (70/30); 0.39 mL, 0.704 mmol) for 10 min at room temperature. After the white slurry turned a clear red color, the solution was cooled to -78 °C and a solution of the aldehyde **66** (0.140 g, 0.704 mmol) in Et_2O (0.6 mL) was added with vigorous stirring. After 5 min, an additional portion of phenyllithium (1.8 M in cyclohexane/Et_2O (70/30); 0.39 mL, 0.704 mmol) was added to the orange slurry. The red solution was stirred for 5 min and ethereal HCl (5.3 M, 0.147 mL, 0.775 mmol) was slowly added followed by a quick addition of potassium *tert*-butoxide[167] (1:1 complex with *tert*-butyl alcohol, 0.197 g, 1.06 mmol). The mixture was warmed to room temperature and stirred for 2 h, then diluted with Et_2O (50 mL), washed with H_2O (4 x 10 mL) until neutral, then brine (1 x 10 mL) and dried ($MgSO_4$). Concentration of the filtrate *in vacuo* gave a yellow liquid, which was purified by flash chromatography (SiO_2; 20% Et_2O in pentane, Rf 0.50) to afford **73** (111 mg, 75%) as a clear oil. This material was contaminated with 2*Z*,4*E*-isomer (8% by ^1H NMR integration), which was not easily removed.

Data for the mixture: $[\alpha]_D^{20}$ -0.63° (*c* 2.06, $CHCl_3$); IR (CH_2Cl_2 cast) 3015 (m), 2953 (s), 2926 (s), 2914 (s), 2878 (s), 1142 (m), 1129 (m), 988 (s) cm^{-1}; MS (CI, NH_3) 228 (MNH_4^+, 8), 211 (MH^+, 57); Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.23; H, 10.55.

Found: C, 74.17; H, 10.23.

Data for the desired *E,E*-diene **73:** ^{1}H NMR a) (400 MHz, benzene-d_6) δ 6.01 (ddt, 1H, *J* = 14.2, 10.2, 1.3 Hz, H-4), 5.98 (ddq, 1H, *J* = 14.2, 10.2, 1.4 Hz, H-3), 5.47 (dt, 1H, *J* = 14.2, 7.3 Hz, H-5), 5.46 (dq, 1H, *J* = 14.2, 6.7 Hz, H-2), 4.77 (t, 1H, *J* = 4.7 Hz, H-2'), 3.98-3.88 (m, 2H, 1 x H-4' & 1 x H-5'), 3.88-3.78 (m, 2H, 1 x H-4' & 1 x H-5'), 2.05 (ddd, 1H, *J* = 13.8, 7.3, 7.0 Hz, 1 x H-6), 1.88 (ddd, 1H, *J* = 13.8, 7.3, 6.5 Hz, 1 x H-6), 1.70-1.55 (m, 2H, H-9), 1.58 (d, 3H, *J* = 6.7 Hz, H-1), 1.55-1.40 (m, 2H, H-7 & 1 x H-8), 1.32-1.18 (m, 1H, 1 x H-8), 0.83 (d, 3H, *J* = 6.4 Hz, 7-C<u>H</u>$_3$); b) (400 MHz, acetone-d_6) δ 6.01 (ddq, 1H, *J* = 14.2, 10.2, 1.4 Hz, H-3), 5.98 (ddt, 1H, *J* = 14.2, 10.2, 1.3 Hz, H-3), 5.55 (dq, 1H, *J* = 14.2, 6.7 Hz, H-2), 5.52 (dt, 1H, *J* = 14.2, 7.3 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.71 (<u>C</u>H=CH), 131.68 (<u>C</u>H=CH), 130.19 (<u>C</u>H=CH), 126.79 (<u>C</u>H=CH), 104.86 (C-2'), 64.86 (C-4' & C-5'), 39.98 (C-6), 33.25 (C-7), 31.57 (<u>C</u>H$_2$), 30.69 (<u>C</u>H$_2$), 19.36 (7-<u>C</u>H$_3$), 17.99 (C-1).



(4*R*)-*E,E*-4-Methyldeca-6,8-dienal (74). Procedure A. A modification of the procedure of Roush and Hall was used.[101] Distilled THF (21.5 mL) and saturated aqueous oxalic acid (15 mL) were added to the protected aldehyde **82** (1.07 g, 5.02 mmol), and the resultant mixture was stirred at room temperature for 24 h, then treated with a further portion of saturated aqueous oxalic acid (2 mL), and stirred for an additional 6 h. The reaction mixture was partitioned between Et_2O (250 mL) and H_2O (50 mL), and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with 5% $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL), and then dried ($MgSO_4$). Partial concentration *in vacuo* gave a volatile pale yellow liquid (0.794 g), which could be used without further purification. A portion of the crude aldehyde (0.200 g) was chromatographed on silica (30% CH_2Cl_2 in pentane, *Rf* 0.25) to

afford **74** (0.156 g, 78%), which still contained the difficult to separate 2*Z*,4*E*-isomer (8% by ^{1}H NMR integration).

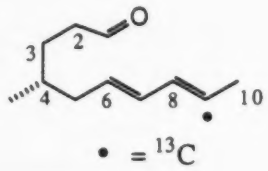
Data for the mixture: $[\alpha]_D^{20}$ -8.27° (*c* 1.28, CH_2Cl_2); IR (CH_2Cl_2 cast) 3015 (m), 2954 (s), 2930 (s), 2725 (m), 1723 (s) cm^{-1}; MS (CI, NH_3) 184 (MNH_4^+, 43), 167 (MH^+, 100); MS (EI) calcd for $C_{11}H_{18}O$ 166.1358, found 166.1357 (M^+, 21), 109.0650 (24); Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.92. Found: C, 79.25; H, 10.88.

Data for the desired *E*,*E*-dienal: ^{1}H NMR (400 MHz, benzene-d_6) δ 9.30 (t, 3H, *J* = 1.7 Hz, H-1), 6.10–5.95 (m, 2H, H-7 & H-8), 5.49 (dq, 1H, *J* = 14.2, 7.1 Hz, H-6), 5.38 (dt, 1H, *J* = 14.1, 7.0 Hz, H-9), 1.95-1.67 (m, 4H, H-2 & H-5), 1.58 (d, 3H, *J* = 7.0 Hz, H-10), 1.44-1.35 (m, 1H, 1 x H-3), 1.25-1.15 (m, 1H, H-4), 1.15-1.07 (m, 1H, 1 x H-3), 0.67 (d, 3H, *J* = 6.7 Hz, 4-C$\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 200.62 (C-1), 132.55 (C$\underline{H}$=CH), 132.25 (C$\underline{H}$=CH), 129.76 (CH=C$\underline{H}$), 126.98 (CH=C$\underline{H}$), 41.58 (C$\underline{H}_2$), 40.31 (C$\underline{H}_2$), 32.97 (C-4), 28.58 (C$\underline{H}_2$), 19.19 (4-C$\underline{H}_3$), 18.04 (C-10).

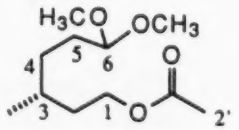
Data for the 2*Z*,4*E*-dienal: ^{1}H NMR (400 MHz, benzene-d_6) δ 9.29 (t, 3H, *J* = 1.7 Hz, H-1), 6.36 (ddq, 1H, *J* = 15.0, 10.2, 1.2 Hz, H-7), 6.10–6.00 (m, 1H, H-8), 5.51 (dt, 1H, *J* = 15.0, 7.4 Hz, H-6), 5.36 (dq, 1H, *J* = 10.8, 7.0 Hz, H-9), 1.95-1.67 (m, 4H, H-2 & H-5), 1.62 (d, 3H, *J* = 7.0 Hz, H-10), 1.44-1.35 (m, 1H, 1 x H-3), 1.25-1.15 (m, 1H, H-4), 1.15-1.07 (m, 1H, 1 x H-3), 0.65 (d, 3H, *J* = 6.8 Hz, 4-C$\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 200.59 (C-1), 132.34 (C$\underline{H}$=CH), 130.01 (C$\underline{H}$=CH), 127.76 (CH=C$\underline{H}$), 124.17 (CH=C$\underline{H}$), 41.58 (C$\underline{H}_2$), 40.31 (C$\underline{H}_2$), 32.92 (C-4), 28.54 (C$\underline{H}_2$), 19.19 (4-C$\underline{H}_3$), 13.34 (C-10).

Procedure B. Distilled THF (25.0 mL) and saturated aqueous oxalic acid (25.0 mL) and formalin (25.0 mL) were added to the protected aldehyde **73** (3.00 g, 14.3 mmol), and the resultant mixture was stirred at room temperature for 24 h. More formalin (10 mL) was added and the solution was stirred for an additional 24 h. The reaction mixture was partitioned between Et_2O (500 mL) and H_2O (100 mL), and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were

washed with 5% $NaHCO_3$ (2 x 100 mL), and brine (50 mL), and dried ($MgSO_4$). Partial concentration *in vacuo* gave a volatile pale yellow liquid (1.80 g, 76%), which could be used without further purification. A portion of the crude mixture (100 mg) was chromatographed on silica (30% CH_2Cl_2 in pentane, R_f 0.25) to afford the aldehyde **74** (66 mg, 50% overall yield) having the same physical and spectral properties as those mentioned above.

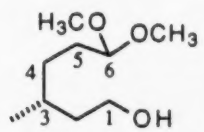


(4*R*)-[9-^{13}C]-*E*,*E*-4-Methyldeca-6,8-dienal (74a). The same method as for the preparation of unlabeled aldehyde **74** was employed. Thus, reaction of labeled acetal **82a** (2.39 g, 11.2 mmol) with saturated aqueous oxalic acid (10 mL) in THF (30 mL) afforded crude **74a** still containing some solvent. Due to the high volatility of the product, this material was used in the next reaction without further purification.



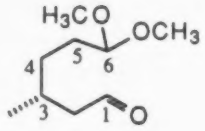
(3*R*)-6,6-Dimethoxy-3-methylhexyl acetate (75). A modification of the procedure of Wenkert and Goodwin was used.[102] A solution of aldehyde **61** (24.3 g, 141 mmol), trimethyl orthoformate (100 mL), and acetyl chloride (0.26 mL, 3.62 mmol) in dry MeOH (100 mL)was heated to reflux overnight using a Dean Stark apparatus. After the solution was allowed to cool, brine (75 mL) and 5% aqueous $NaHCO_3$ (75 mL) were added. Most of the MeOH was removed *in vacuo* and the mixture was extracted with Et_2O (2 x 350 mL). The Et_2O layer was washed with H_2O (50 mL) and brine (50 mL), and these aqueous washings were combined and back-extracted with Et_2O (3 x 250 mL). The

combined Et_2O fractions were dried ($MgSO_4$) and concentrated *in vacuo* to a clear colourless oil (31.8 g), which can be used without further purification. A small portion (0.638 g) was removed and purified by Kugelrohr distillation to yield a clear oil **75** (0.580 g, 91%): bp 109-111 °C (0.2 mm Hg); $[\alpha]_D^{20}$ +2.23° (*c* 2.38, $CHCl_3$); IR ($CHCl_3$ cast) 2955 (m), 2934 (m), 1741 (s), 1240 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (t, 1H, *J* = 4.7 Hz, H-6), 4.13-4.04 (m , 2H, H-1), 3.30 (s, 6H, 2 x $OC\underline{H}_3$), 2.03 (s, 3H, H-2'), 1.70-1.50 (m, 4H, 1 x H-2, & H-3 & H-5), 1.49-1.32 (m, 2H, 1 x H-2 & 1 x H-4), 1.24-1.14 (m, 1H, 1 x H-4), 0.90 (d, 3H, *J* = 6.5 Hz, 3-$C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.18 (C-1'), 104.86 (C-6), 62.91 (C-1), 52.69 (2 x $O\underline{C}H_3$), 35.47 ($\underline{C}H_2$), 31.58 ($\underline{C}H_2$), 30.01 ($\underline{C}H_2$), 29.81 (C-3), 21.02 (C-2'), 19.41 (3-$\underline{C}H_3$); MS (CI, NH_3) 236 (MNH_4^+, 6); Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.51; H, 10.16. Found: C, 60.20; H, 10.40.

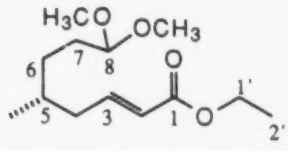


(3*R*)-6,6-Dimethoxy-3-methylhexanol (76). Freshly prepared sodium methoxide (0.47 g, 8.7 mmol) was added to a solution of acetate **75** (20.0 g, 91.5 mmol) in dry MeOH (200 mL). After stirring at room temperature overnight, the mixture was treated with H_2O (120 mL), and the solvent volume was reduced *in vacuo* to give an aqueous residue, which was extracted with Et_2O (3 x 330 mL). The combined Et_2O fractions were washed with H_2O (2 x 100 mL) and brine (200 mL), and these aqueous washings were back-extracted with Et_2O (3 x 50 mL). The combined Et_2O fractions were again washed with H_2O (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a clear colourless oil (14.4 g), which could be used without further purification. A small portion (0.948 g) was removed and purified by Kugelrohr distillation to yield a clear oil **76** (0.844 g, 89%): bp 125 °C (0.1 mm Hg); $[\alpha]_D^{20}$ +2.75° (*c* 2.22,

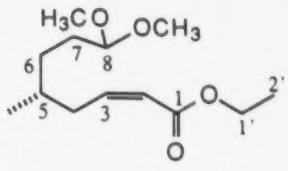
$CHCl_3$); IR ($CHCl_3$ cast) 3409 (br m), 2953 (s), 2929 (s), 2873 (m), 1129 (m), 1059 (s) cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 4.26 (t, 1H, J = 5.7 Hz, H-6), 3.57-3.40 (m, 2H, H-1), 3.13 (s, 6H, 2 x $OC\underline{H}_3$), 1.70-1.49 (m, 4H, 1 x H-2 & H-3 & H-5), 1.49-1.32 (m, 1H, 1 x H-2), 1.32-1.12 (m, 2H, H-4), 0.83 (d, 3H, J = 6.6 Hz, 3-$C\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 104.91 (C-6), 60.61 (C-1), 52.25 ($OC\underline{H}_3$), 52.10 ($OC\underline{H}_3$), 40.10 ($\underline{C}H_2$), 32.08 ($\underline{C}H_2$), 30.24 ($\underline{C}H_2$), 29.60 (C-3), 19.73 (3-$\underline{C}H_3$); MS (CI, NH_3) 194 (MNH_4^+, 2.7), 177 (MH^+, 0.1), 130 (100); Anal. Calcd for $C_9H_{20}O_3$: C, 61.31; H, 11.44. Found: C, 60.94; H, 11.29.



(3*R*)-6,6-Dimethoxy-3-methylhexanal (77). The same procedure for the formation of aldehyde **64** was used. Thus, oxidation of alcohol **76** (13.9 g, 78.8 mmol) with DMSO (11.2 mL, 158 mmol) and oxalyl chloride (8.24 mL, 94.5 mmol) afforded a pale yellow oil (13.0 g) which could be used without further purification. A small portion (1.50 g) was removed and purified by flash chromatograghy (SiO_2; 25% Et_2O in pentane, R_f 0.25) to yield **77** (1.28 g, 85%) as an oil: $[\alpha]_D^{20}$ +13.23° (c 1.41, $CHCl_3$); IR (neat) 2955 (s), 2935 (s), 2880 (s), 2831 (s), 2720 (m), 1725 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, 1H, J = 2.2 Hz, H-1), 4.30 (t, 1H, J = 5.6 Hz, H-6), 3.27 (s, 6H, 2 x $OC\underline{H}_3$), 2.38 (ddd, 1H, J = 16.0, 5.8, 2.2 Hz, 1 x H-2), 2.21 (ddd, 1H, J = 16.0, 7.8, 2.2 Hz, 1 x H-2), 2.04 (br p, 1H, J = 6.6 Hz, H-3), 1.71-1.48 (m, 2H, H-5), 1.41-1.12 (m, 2H, H-4), 0.93 (d, 3H, J = 6.7 Hz, 3-$C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.54 (C-1), 104.55 (C-6), 52.78 ($OC\underline{H}_3$), 52.74 ($OC\underline{H}_3$), 50.92 (C-2), 31.52 ($\underline{C}H_2$), 29.99 ($\underline{C}H_2$), 27.94 (C-3), 19.80 (3-$\underline{C}H_3$); MS (CI, NH_3) 192 (MNH_4^+, 8), 175 (MH^+, 0.4), 75 (100); Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.89; H, 10.14.



78



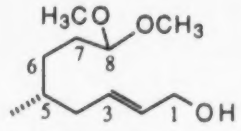
79

Ethyl (5*R*)-*E*-8,8-Dimethoxy-5-methyloct-2-enoate (78) and its Z-isomer 79. A modification of the method of Seebach and coworkers was used.[104] A solution of aldehyde **77** (31.2 g, 179 mmol) and (carbethoxymethylene)triphenyl phosphorane (**68**) (77.1 g, 221 mmol) in dry benzene (1500 mL) was heated to reflux at 85 °C for 12 h. The mixture was cooled, the solvent was removed *in vacuo* and the residue was purified by repeated flash chromatography (SiO_2; 15% Et_2O in pentane) to yield the desired *E*-isomer **78** (29.9 g, 68%, R_f 0.14) together with the minor, *Z*-isomer **79** (5.29 g, 10%, R_f 0.19). A small portion of the *E*-isomer was removed and purified further by Kugelrohr distillation to give a clear oil.

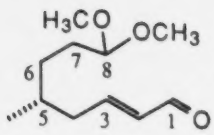
Data for *E*-isomer **78:** bp 148-151 °C (0.75 mm Hg); $[\alpha]_D^{20}$ +2.98° (*c* 1.98, $CHCl_3$); IR (CH_2Cl_2 cast) 2956 (m), 2931 (m), 1722 (s), 1654 (m) cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.03 (dt, 1H, *J* = 15.5, 7.7 Hz, H-3), 5.87 (dt, 1H, *J* = 15.5, 1.2 Hz, H-2), 4.19 (t, 1H, *J* = 5.7 Hz, H-8), 4.04 (q, 2H, *J* = 7.1 Hz, H-1'), 3.12 (s, 6H, 2 x $OC\underline{H}_3$), 1.85 (dddd, 1H, *J* = 13.0, 7.7, 5.3, 1.2 Hz, 1 x H-4), 1.67 (dddd, 1H, *J* = 13.0, 7.7, 7.7, 1.2 Hz, 1 x H-4), 1.60-1.50 (m, 1H, 1 x H-7), 1.50-1.40 (m, 1H, 1 x H-7), 1.32-1.20 (m, 2H, H-5 & 1 x H-6), 1.11-1.02 (m, 1H 1 x H-6), 0.98 (t, 3H, *J* = 7.1 Hz, H-2'), 0.67 (d, 3H, *J* = 6.6 Hz, 5-$C\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 166.05 (C-1), 147.70 (C-3), 123.11 (C-2), 104.66 (C-8), 59.97 (C-1'), 52.21 (2 x $OC\underline{H}_3$), 39.57 (C-4), 32.49 (C-5), 31.64 ($\underline{C}H_2$), 30.26 ($\underline{C}H_2$), 19.39 (5-$\underline{C}H_3$), 14.30 (C-2'); MS (CI, NH_3) 262 (MNH_4^+, 27), 198 (100); Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.89; H, 9.91. Found: C, 63.92; H, 9.92.

Data for *Z*-isomer **79:** IR (CH_2Cl_2 cast) 2954 (s), 2932 (s), 2876 (m), 2831 (m), 1740 (m), 1721 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (dt, 1H, *J* = 11.6, 7.5 Hz,

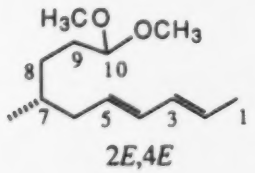
H-3), 5.79 (dt, 1H, J = 11.6, 1.7 Hz, H-2), 4.32 (t, 1H, J = 5.7 Hz, H-8), 4.15 (q, 2H, J = 7.0 Hz, H-1'), 3.30 (s, 6H, 2 x OC$\underline{H}_3$), 2.70-2.49 (m, 2H, H-4), 1.70-1.50 (m, 3H, H-5 & H-7), 1.45-1.35 (m, 2H, H-6), 1.27 (t, 3H, J = 7.0 Hz, H-2'), 0.91 (d, 3H, J = 6.7 Hz, 5-C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.25 (C-1), 148.81 (C-3), 120.45 (C-2), 104.66 (C-8), 59.57 (C-1'), 52.41 (2 x O$\underline{C}H_3$), 35.73 (C-4), 33.09 (C-5), 31.24 ($\underline{C}H_2$), 29.93 ($\underline{C}H_2$), 19.34 (5-$\underline{C}H_3$), 14.14 (C-2'); MS (CI, NH_3) 262 (MNH_4^+, 20), 245 (MH^+, 0.3), 246 (22.8), 198 (100).



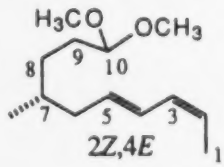
(5*R*)-*E*-8,8-Dimethoxy-5-methyloct-2-enol (80). The same method as for the preparation of allylic alcohol **71** was employed. Thus, reduction of ester **78** (8.10 g, 33.2 mmol) with DIBAL (17.7 mL, 99.5 mmol) afforded **80** (5.39 g, 80%) as a clear oil after flash chromatography (SiO_2; 50 x 250 mm, 75% Et_2O in pentane, R_f 0.31): $[\alpha]_D^{20}$ +3.42° (c 2.93, $CHCl_3$); IR (CH_2Cl_2 cast) 3420 (br m), 2952 (s), 2930 (s), 1458 (m), 1384 (m) cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 5.55-5.49 (m, 2H, H-2 & H-3), 4.27 (t, 1H, J = 5.6 Hz, H-8), 3.91 (br s, 2H, H-1), 3.14 (s, 6H, 2 x OC$\underline{H}_3$), 1.99-1.90 (m, 1H, 1 x H-4), 1.84-1.75 (m, 1H, 1 x H-4), 1.70-1.50 (m, 3H, OH & H-7) 1.45-1.33 (m, 2H, H-5 & 1 x H-6), 1.22-1.12 (m, 1H, 1 x H-6), 0.82 (d, 3H, J = 6.5 Hz, 5-C$\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 131.57 & 130.19 ($\underline{C}H$=$\underline{C}H$), 104.88 (C-8), 63.41 (C-1), 52.24 (2 x O$\underline{C}H_3$), 39.91 (C-4), 33.12 (C-5), 31.53 ($\underline{C}H_2$), 30.36 ($\underline{C}H_2$), 19.59 (5-$\underline{C}H_3$); MS (CI, NH_4) 220 (MNH_4^+, 6), 203 (MH^+, 0.3); Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.30; H, 10.97. Found: C, 65.40; H, 11.07.



(5*R*)-*E*-8,8-Dimethoxy-5-methyloct-2-enal (81). The same method as for the preparation of aldehyde **66** was employed. Thus, oxidation of alcohol **80** (4.66 g, 23.1 mmol) with DMSO (3.11 mL, 43.8 mmol) and oxalyl chloride (2.41 mL, 27.7 mmol) afforded **81** (4.04 g, 94%, based on 7% recovered starting material) as a clear oil after flash chromatography (SiO_2; 50% Et_2O in pentane, *Rf* 0.35): $[\alpha]_D^{20}$ -0.20° (*c* 2.50, $CHCl_3$); IR (CH_2Cl_2 cast) 2954 (m), 2932 (m), 2725 (w), 1693 (s), 1636 (w) cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 9.30 (d, 1H, *J* = 7.7 Hz, H-1), 6.09 (dt, 1H, *J* = 15.5, 7.7 Hz, H-3), 5.90 (ddt, 1H, *J* = 15.5, 7.7, 1.0 Hz, H-2), 4.21 (t, 1H, *J* = 5.5 Hz, H-8), 3.14 (s, 6H, 2 x $OC\underline{H}_3$), 1.76 (ddd, 1H, *J* = 13.4, 7.7, 5.8 Hz, 1 x H-4), 1.59 (ddd, 1H, *J* = 13.4, 7.7, 7.4 Hz, 1 x H-4), 1.56-1.40 (m, 2H, H-7), 1.28-1.15 (m, 2 H, H-5 & 1 x H-6), 1.10-0.99 (m, 1H, 1 x H-6), 0.61 (d, 3H, *J* = 6.3 Hz, 5-$C\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 192.57 (C-1), 155.71 (C-3), 134.51 (C-2), 104.65 (C-8), 52.35 (2 x $O\underline{C}H_3$), 39.77 (C-4), 32.37 (C-5), 31.53 ($\underline{C}H_2$), 30.76 ($\underline{C}H_2$), 19.33 (5-$\underline{C}H_3$); MS (CI, NH_3) 218 (MNH_4^+, 25), 201 (MH^+, 0.1), 75 (100); Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.95; H, 10.07. Found: C, 65.81; H, 10.09.



2*E*,4*E*



2*Z*,4*E*

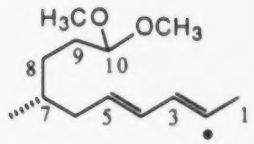
(7*R*)-*E*,*E*-10,10-Dimethoxy-7-methyldeca-2,4-diene (82). The same method as for the preparation of diene **73** was employed. Thus, condensation of aldehyde **81** (1.46 g, 7.29 mmol) with ethyltriphenylphosphonium iodide (**72**) (3.05 g, 7.29 mmol) afforded **82** (1.18 g, 76%) as a clear oil after flash chromatography (SiO_2; 5% Et_2O in pentane, *Rf* 0.30). This material was contaminated with the 2*Z*,4*E*-isomer (8% by

^{1}H NMR integration), which was difficult to remove.

Data for the mixture: $[\alpha]_D^{20}$ -3.22° (*c* 2.39, $CHCl_3$); IR (CH_2Cl_2 cast) 3016 (m), 2952 (s), 2929 (s), 1457 (m), 1378 (m) cm^{-1}; MS (CI, NH_3) 230 (MNH_4^+, 1.0), 213 (MH^+, 0.1); Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.52; H, 11.40. Found: C, 73.76; H, 11.46.

Data for the desired *E*,*E*-diene: ^{1}H NMR (400 MHz, benzene-d_6) δ 6.12–5.99 (m, 2H, H-3 & H-4), 5.53–5.43 (m, 2H, H-2 & H-5), 4.28 (t, 1H, *J* = 5.7 Hz, H-10), 3.15 (s, 6H, 2 x OCH_3), 2.04 (ddd, 1H, *J* = 13.8, 7.0, 7.0 Hz, 1 x H-6), 1.87 (ddd, 1H, *J* = 13.8, 7.0, 6.5 Hz, 1 x H-6), 1.72-1.52 (m, 2H, H-9), 1.62 (d, 3H, *J* = 6.7 Hz, H-1), 1.48-1.38 (m, 2H, H-7 & 1 x H-8), 1.27-1.18 (m, 1H, 1 x H-8), 0.83 (d, 3H, *J* = 6.6 Hz, 7-CH_3); ^{13}C NMR (100 MHz, benzene-d_6) δ 132.46 (C-3), 132.40 (C-4), 130.34 (C-5), 126.68 (C-2), 104.88 (C-10), 52.07 (2 x OCH_3), 40.38 (C-6), 33.55 (C-7), 31.73 (CH_2), 30.48 (CH_2), 19.65 (7-CH_3), 18.08 (C-1).

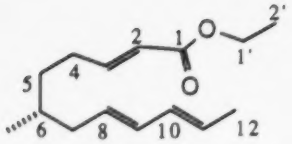
Data for the 2*Z*,4*E*-diene: ^{1}H NMR (400 MHz, benzene-d_6) δ 6.42 (ddt, 1H, *J* = 15.0, 10.9, 1.2 Hz, H-4), 6.11–6.05 (m, 1H, H-3), 5.59 (dt, 1H, *J* = 15.0, 7.4 Hz, H-5), 5.35 (dq, 1H, *J* = 10.8, 7.4 Hz, H-2), 4.25 (t, 1H, *J* = 5.9 Hz, H-10), 3.15 (s, 6H, 2 x OCH_3), 2.08 (ddd, 1H, *J* = 13.8, 7.4, 7.0 Hz, 1 x H-6), 1.87 (ddd, 1H, *J* = 13.8, 7.4, 6.5 Hz, 1 x H-6), 1.72-1.52 (m, 2H, H-9), 1.65 (d, 3H, *J* = 7.4 Hz, H-1), 1.48-1.38 (m, 2H, H-7 & 1 x H-8), 1.28-1.15 (m, 1H, 1 x H-8), 0.82 (d, 3H, *J* = 6.7 Hz, 7-CH_3); ^{13}C NMR (100 MHz, benzene-d_6) δ 132.93 (CH=CH), 130.23 (CH=CH), 127.32 (CH=CH), 123.90 (CH=CH), 104.88 (C-10), 52.17 (2 x OCH_3), 40.66 (C-6), 33.55 (C-7), 31.76 (CH_2), 30.48 (CH_2), 19.65 (7-CH_3), 13.33 (C-1).



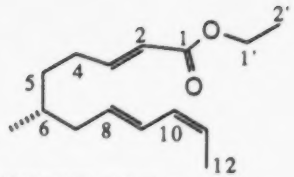
• = ^{13}C

(7*R*)-[2-^{13}C]-*E*,*E*-10,10-Dimethoxy-7-methyldeca-2,4-diene (82a). The same method as for the preparation of **73** was employed, except [1-^{13}C]-ethyltriphenylphosphonium iodide (**72a**) (5.55 g, 13.2 mmol) (isotopic purity 99% ^{13}C) was used. Thus, aldehyde **81** (2.92 g, 14.6 mmol) afforded diene **82a** (2.40 g, 85%) as a clear oil after flash chromatography (SiO_2; 5% Et_2O in pentane, R_f 0.30). This material was contaminated with the 2*Z*,4*E*-isomer (8% by NMR integration), which was difficult to remove.

Data for the *E*,*E*-isomer: ^{1}H NMR (400 MHz, benzene-d_6) δ 6.12–5.95 (m, 2H, H-3 & H-4), 5.49 (m, 1H, H-5), 5.52-5.46 (ddd, 1H, J = 150.5, 14.1, 6.7 Hz, H-2), 4.28 (t, 1H, J = 5.7 Hz, H-10), 3.15 (s, 6H, 2 x OC$\underline{H}_3$), 2.04 (ddd, 1H, J = 13.8, 7.0, 7.0 Hz, 1 x H-6), 1.87 (ddd, 1H, J = 13.8, 7.0, 6.5 Hz, 1 x H-6), 1.72-1.52 (m, 2H, H-9), 1.62 (dd, 3H, J = 6.7, 6.7 Hz, H-1), 1.48-1.38 (m, 2H, H-7 & 1 x H-8), 1.27-1.18 (m, 1H, 1 x H-8), 0.85 (d, 3H, J = 6.6 Hz, 7-C$\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 132.42 (d, J = 71.4 Hz, C-3), 132.36 (C-4), 130.30 (d, J = 10.0 Hz, C-5), 126.64 (C-2), 104.85 (C-10), 52.14 (O$\underline{C}H_3$), 52.03 (O$\underline{C}H_3$), 40.35 (C-6), 33.48 (C-7), 31.69 ($\underline{C}H_2$), 30.44 ($\underline{C}H_2$), 19.62 (7-$\underline{C}H_3$), 18.03 (C-1).



(2*E*,8*E*,10*E*) 83



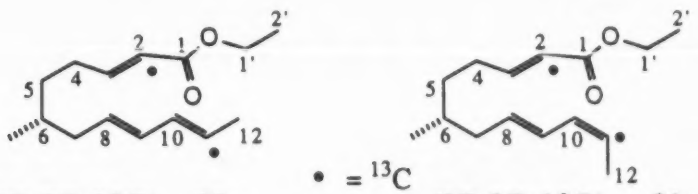
(2*E*,8*E*,10*Z*) 84

Ethyl (6*R*)-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoate (83). A modification of the method of Seebach and coworkers was used.[104] A solution of aldehyde **74** (1.25 g, 7.54 mmol) and (carbethoxymethylene) triphenylphosphorane (**68**) (3.15 g, 9.04 mmol) in dry benzene (150 mL) was heated to reflux at 85 °C for 17 h. The mixture was cooled to room temperature and the solvent was removed *in vacuo* to give a pale yellow slurry. The slurry was partially purified on flash silica (40 x 220 mm, 5% Et_2O in pentane, R_f 0.41) to yield a mixture of trienes (1.42 g, 80%). This oil was separated using MPLC with $AgNO_3$-stained silica gel, to give the 2*E*,8*E*,10*Z*-triene impurity **84** (126 mg, 7%), the desired *E*,*E*,*E*-triene **83** (1.11 g, 62%), and some mixed material (95.8 mg, 5%). The *E*,*E*,*E*-triene was further purified on flash silica (5% Et_2O in pentane, R_f 0.41) to yield **83** (834 mg, 47%) as a clear oil.

Data for the *E*,*E*,*E*-triene **83**: $[\alpha]_D^{20}$ -7.59° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$ cast) 3016 (w), 2957 (m), 2927 (m), 2914 (m), 2872 (w), 2853 (w), 1722 (s), 1655 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, 1H, *J* = 15.6, 6.9 Hz, H-3), 6.02 (ddq, 1H, *J* = 14.2, 10.4, 1.5 Hz, H-10), 5.97 (ddt, 1H, *J* = 14.4, 10.4, 1.3 Hz, H-9), 5.81 (dt, 1H, *J* = 15.6, 1.6 Hz, H-2), 5.58 (dq, 1H, *J* = 14.2, 6.9 Hz, H-11), 5.50 (dt, 1H, *J* = 14.4, 7.3 Hz, H-8), 4.17 (q, 2H, *J* = 6.5 Hz, H-1'), 2.29-2.10 (m, 2H, H-4), 2.06 (ddd, 1H, *J* = 13.5, 7.3, 6.1 Hz, 1 x H-7), 1.93 (ddd, 1H, *J* = 13.5, 7.3, 7.0 Hz, 1 x H-7), 1.73 (d, 3H, *J* = 6.9 Hz, H-12), 1.56-1.43 (m, 2H, 1 x H-5 & H-6), 1.28-1.19 (m, 1H, 1 x H-5), 1.28 (t, 3H, *J* = 6.5 Hz, H-2'), 0.90 (d, 3H, *J* = 6.4 Hz, 6-$C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.81 (C-1), 149.48 (C-3), 131.89 (C-9), 131.60 (C-10), 129.90 (C-8), 127.14 (C-11), 121.23 (C-2), 60.16 (C-1'), 39.93 (C-7), 34.69 (C-5), 32.79 (C-6), 29.86 (C-4), 19.32 (6-$\underline{C}H_3$), 18.02 (C-12), 14.31 (C-2'); MS (EI) calcd for $C_{15}H_{24}O_2$

236.1776, found 236.1775 (M^+, 9), 190.1353 (6); Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.21; H, 10.24. Found: C, 76.40; H, 10.22.

Data for the 2*E*,4*E*,10*Z*-isomer **84**: $[\alpha]_D^{20}$ -13.5° (*c* 0.93, CH_2Cl_2); IR (CH_2Cl_2 cast) 3019 (w), 2978 (m), 2957 (m), 2917 (m), 2872 (w), 1722 (s), 1655 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.95 (dt, 1H, *J* = 15.6, 6.9 Hz, H-3), 6.31 (ddt, 1H, *J* = 15.0, 10.9, 1.1 Hz, H-10), 6.08–5.88 (m, 1H, H-9), 5.81 (dt, 1H, *J* = 15.6, 1.5 Hz, H-2), 5.59 (dt, 1H, *J* = 15.0, 7.1 Hz, H-8), 5.37 (dq, 1H, *J* = 10.8, 6.6 Hz, H-11), 4.18 (q, 2H, *J* = 7.1 Hz, H-1'), 2.35-2.20 (m, 2H, H-4), 2.20-1.85 (m, 2H, H-7), 1.73 (d, 3H, *J* = 6.6 Hz, H-12), 1.67-1.40 (m, 2H, 1 x H-5 & H-6), 1.40-1.20 (m, 1H, 1 x H-5), 1.28 (t, 3H, *J* = 7.1 Hz, H-2'), 0.90 (d, 3H, *J* = 6.8 Hz, 6-$\underline{C}H_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 166.15 (C-1), 149.09 (C-3), 132.50 (C-9), 130.08 (C-10), 127.76 (C-8), 124.05 (C-11), 121.62 (C-2), 59.95 (C-1'), 40.40 (C-7), 34.92 (C-5), 32.89 (C-6), 29.88 (C-4), 19.22 (6-$\underline{C}H_3$), 14.33 (C-2'), 13.31 (C-12); MS (EI) calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1774 (M^+, 9), 191.1426 (7).



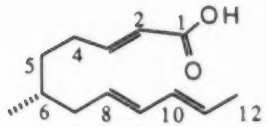
(2*E*,8*E*,10*E*) 83a **(2*E*,8*E*,10*Z*) 84a**

Ethyl (6*R*)-[2,11-$^{13}C_2$]-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoate (83a). The same method as for the preparation of unlabeled triene ethyl ester **83** was employed, except [2-^{13}C]-(carbethoxymethylene)triphenylphosphorane (**68a**) (3.91 g, 11.2 mmol) (isotopic purity 99% ^{13}C) was used. Thus, labeled aldehyde **74a** (1.87 g, 11.2 mmol) afforded the desired *E*,*E*,*E*-isomer **83a** (992 mg, 53%) and the 2*E*,8*E*,10*Z*-isomer **84a** (160 mg, 6%).

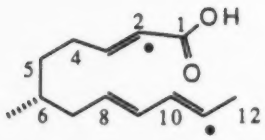
Data for *E*,*E*,*E*-isomer **83a**: $[\alpha]_D^{20}$ -7.80° (*c* 0.41, CH_2Cl_2); IR (CH_2Cl_2 cast) 3006 (w), 2980 (w), 2957 (m), 2928 (m), 2914 (m), 2873 (w), 2854 (w), 1721 (s), 1628 (m),

1260 (m), 1046 (m) cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.03 (dtd, 1H, *J* = 15.7, 7.0, 2.0 Hz, H-3), 6.08–5.96 (m, 2H, H-9 & H-10), 5.87 (ddt, 1H, *J* = 161.1, 15.7, 1.6 Hz, H-2), 5.52 (ddq, 1H, *J* = 150.5, 14.2, 7.0 Hz, H-11), 5.40 (dt, 1H, *J* = 14.2, 7.0 Hz, H-8), 4.05 (q, 2H, *J* = 7.1 Hz, H-1'), 1.92-1.70 (m, 4H, H-4 & H-7), 1.60 (dd, 3H, *J* = 7.0, 7.0 Hz, H-12), 1.30-1.15 (m, 2H, 1 x H-5 & H-6), 0.99 (t, 3H, *J* = 7.1 Hz, H-2'), 1.02-0.92 (m, 1H, 1 x H-5), 0.71 (d, 3H, *J* = 6.6 Hz, 6-C$\underline{H}_3$); ^{13}C NMR (100 MHz, benzene-d_6) δ 166.81 (d, *J* = 75.5 Hz, C-1), 149.10 (d, *J* = 69.4 Hz, C-3), 132.49 (C-9), 132.31 (d, *J* = 71.4 Hz, C-10), 129.95 (C-8), 127.04 (C-11), 121.81 (C-2), 59.95 (C-1'), 40.12 (C-7), 34.88 (d, *J* = 3.0 Hz, C-4), 32.92 (C-6), 29.88 (C-5), 19.23 (6-$\underline{C}H_3$), 18.04 (d, *J* = 43.3 Hz, C-12), 14.34 (C-2'); MS (EI) calcd for $^{13}C_2{}^{2}C_{13}H_{24}O_2$ 238.1843, found 238.1834 (M^+, 7), 209.1447 (1.1), 165.1548 (30); Anal. Calcd for $^{13}C_2{}^{2}C_{13}H_{24}O_2$: C, 76.42; H, 10.15. Found: C, 76.21; H, 10.14.

Data for 2*E*,8*E*,10*Z*-isomer **84a**: $[\alpha]_D^{20}$ -11.9° (*c* 1.33, CH_2Cl_2); IR (CH_2Cl_2 cast) 3014 (w), 2980 (m), 2957 (m), 2916 (m), 2772 (w), 1721 (s), 1628 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (ddt, 1H, *J* = 15.6, 6.9, 1.9 Hz, H-3), 6.31 (dddt, 1H, *J* = 15.0, 10.9, 1.3, 1.1 Hz, H-9), 5.95 (dddd, 1H, *J* = 10.9, 10.8, 1.7, 1.4 Hz, H-10), 5.79 (ddt, 1H, *J* = 162.0, 15.6, 1.6 Hz, H-2), 5.59 (dt, 1H, *J* = 15.0, 7.1 Hz, H-8), 5.36 (ddq, 1H, *J* = 154.8, 10.8, 7.1 Hz, H-11), 4.16 (q, 2H, *J* = 7.2 Hz, H-1'), 2.30-2.13 (m, 2H, H-4), 2.08 (ddd, 1H, *J* = 14.2, 7.1, 6.4 Hz, 1 x H-7), 1.95 (ddd, 1H, *J* = 14.2, 7.2, 7.1 Hz, 1 x H-7), 1.71 (ddd, 3H, *J* = 7.1, 7.0, 1.7 Hz, H-12), 1.57-1.44 (m, 2H, 1 x H-5 & H-6), 1.30-1.20 (m, 1H, 1 x H-5), 1.26 (t, 3H, *J* = 7.2 Hz, H-2'), 0.88 (d, 3H, *J* = 6.6 Hz, 6-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.67 (d, *J* = 75.0 Hz, C-1), 149.30 (d, *J* = 71.0 Hz, C-3), 132.22 (C-9), 129.39 (d, *J* = 71.0 Hz, C-10), 127.01 (C-8), 124.14 (C-11), 121.23 (C-2), 60.07 (C-1'), 40.18 (C-7), 34.71 (d, *J* = 2.9 Hz, C-4), 32.74 (C-6), 29.79 (C-5), 19.28 (6-$\underline{C}H_3$), 14.23 (C-2'), 13.25 (d, *J* = 42.9 Hz, C-12); MS (EI) calcd for $^{13}C_2{}^{12}C_{15}H_{24}O_2$ 238.1843, found 238.1841 (M^+, 7), 193.1498 (7), 165.1551 (31).

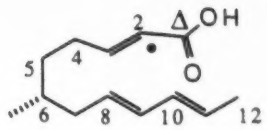


(6*R*)-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoic Acid (85). A modification of the ester hydrolysis method of Seebach and coworkers was used.[104] A solution of triene ethyl ester **83** (1.00 g, 4.23 mmol) in distilled THF (50 mL) was treated with aqueous 3M KOH (10 mL), and the mixture was stirred for 18 h at 50 °C. Most of the THF was removed *in vacuo*, and the cloudy solution was stirred at 50 °C until it became clear. After cooling, H_2O (500 mL) was added and this solution was washed with pentane (2 x 50 mL). The aqueous layer was acidified to pH 7 (1N HCl) and then extracted with Et_2O (3 x 200 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to yield a clear oil (855 mg, 97%), which could be used without further purification. The acid could be purified by flash chromatography (SiO_2; 20 x 250 mm, 100% Et_2O, R_f 0.50) to yield **85** (656 mg, 75%) as a clear oil: $[\alpha]_D^{20}$ -7.37° (*c* 0.095, $CHCl_3$); IR ($CHCl_3$ cast) 3400-2300 (br), 3016 (s), 2958 (s), 2914 (s), 1696 (s), 1650 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.2 (br s, 1H, COO<u>H</u>), 7.08 (dt, 1H, *J* = 15.6, 6.9 Hz, H-3), 6.02 (ddq, 1H, *J* = 14.2, 10.4, 1.5 Hz, H-10), 5.98 (ddt, 1H, *J* = 14.4, 10.4, 1.3 Hz, H-9), 5.82 (dt, 1H, *J* = 15.6, 1.6 Hz, H-2), 5.58 (dq, 1H, *J* = 14.2, 6.9 Hz, H-11), 5.50 (dt, 1H, *J* = 14.4, 7.3 Hz, H-8), 2.34-2.14 (m, 2H, H-4), 2.05 (ddd, 1H, *J* = 13.8, 7.3, 6.4 Hz, 1 x H-7), 1.93 (ddd, 1H, *J* = 13.8, 7.3, 7.0 Hz, 1 x H-7), 1.73 (d, 3H, *J* = 6.9 Hz, H-12), 1.57-1.45 (m, 2H, 1 x H-5 & H-6), 1.32-1.22 (m, 1H, 1 x 1 x H-5), 0.88 (d, 3H, *J* = 6.6 Hz, 6-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.28 (C-1), 152.49 (C-3), 131.96 (C-9), 131.59 (C-10), 129.76 (C-8), 127.16 (C-11), 120.63 (C-2), 39.90 (C-7), 34.50 (C-4), 32.82 (C-6), 29.98 (C-5), 19.30 (6-<u>C</u>H$_3$), 18.03 (C-12); MS (CI, NH_3) 226 (MNH_4^+, 81), 209 (MH^+, 6); Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.61; H, 9.73.



• = ^{13}C

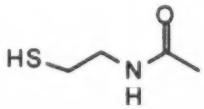
(6*R*)-[2,11-$^{13}C_2$]-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoic Acid (85a). The same method as for the preparation of unlabeled triene acid **85** was employed. Thus, hydrolysis of labeled triene ethyl ester **83a** (170 mg, 7.13 mmol) with 3M KOH (7 mL) in THF (2 mL) afforded **85a** (111 mg, 74%) as a clear oil: $[\alpha]_D^{20}$ -8.28° (*c* 1.22, CH_2Cl_2); IR (CH_2Cl_2 cast) 3400-2400 (br m), 3007 (m), 2957 (m), 2915 (m), 2876 (m), 2854 (m), 1692 (s), 1626 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.2 (br s, 1H, COO<u>H</u>), 7.07 (dtd, 1H, *J* = 15.6, 7.0, 1.9 Hz, H–3), 6.05–5.92 (m, 2H, H-9 & H-10), 5.82 (ddt, 1H, *J* = 162.8, 15.6, 1.4 Hz, H-2), 5.59 (ddq, 1H, *J* = 150.2, 14.2, 6.9 Hz, H-11), 5.50 (dt, 1H, *J* = 14.2, 7.3 Hz, H-8), 2.34-2.14 (m, 2H, H-4), 2.05 (ddd, 1H, *J* = 13.8, 7.3, 6.4 Hz, 1 x H-7), 1.93 (ddd, 1H, *J* = 13.8, 7.3, 7.0 Hz, 1 x H-7), 1.73 (dd, 3H, *J* = 6.9, 6.8 Hz, H-12), 1.57-1.45 (m, 2H, 1 x H-5 & H-6), 1.32-1.22 (m, 1H, 1 x H-5), 0.89 (d, 3H, *J* = 6.6 Hz, 6-C<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.30 (d, *J* = 69.8 Hz, C-1), 152.46 (d, *J* = 69.4 Hz, C-3), 131.98 (C-9), 131.64 (d, *J* = 70.9 Hz, C-10), 129.75 (C-8), 127.15 (C-11), 120.66 (C-2), 39.91 (C-7), 34.54 (d, *J* = 3.5 Hz, C-4), 32.85 (C-6), 30.00 (C-5), 19.32 (6-<u>C</u>H$_3$), 18.01 (d, *J* = 43.8 Hz, C-12); MS (EI) calcd for $^{13}C_2{}^2C_{11}H_{20}O_2$ 210.1536, found 210.1527 (M^+, 4.3), 165.1548 (19); Anal. Calcd for $^{13}C_2{}^2C_{11}H_{20}O_2$: C, 75.20; H, 9.59. Found: C, 74.91; H, 9.44.



• = ^{13}C

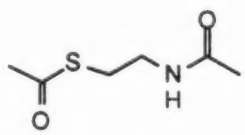
Δ = $^{13/14}C$

30:70 Mixture of [1,2-$^{13}C_2$, 1-^{14}C] : [2-$^{13}C_2$, 1-^{14}C]-(6*R*)-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoic Acid (85b). The same method as for the preparation of unlabeled triene acid **85** was employed. Thus, hydrolysis of labeled triene ethyl ester **161** (450 mg, 1.95 mmol) with 3M KOH (7 mL) in THF (2 mL) afforded **85b** (415 mg, 98%) still containing the 2*E*,8*E*,10*Z*-isomer (11% by ^1H NMR integration): ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.02 (m, 1H, H-3), 6.08–5.94 (m, 2H, H-9 & H-10), 5.85 (dm, 1H, *J* = 162.0 Hz, H-2), 5.61 (dq, 1H, *J* = 14.2, 7.0 Hz, H-11), 5.52 (dt, 1H, *J* = 14.2, 6.9 Hz, H-8), 2.33-2.17 (m, 2H, H-4), 2.07 (ddd, 1H, *J* = 13.9, 6.8, 6.5 Hz, 1 x H-7), 1.94 (ddd, 1H, *J* = 13.8, 7.1, 7.0 Hz, 1 x H-7), 1.73 (d, 3H, *J* = 6.8 Hz, H-12), 1.56-1.46 (m, 2H, 1 x H-5 & H-6), 1.33-1.24 (m, 1H, 1 x H-5), 0.89 (d, 3H, *J* = 6.6 Hz, 6-C$\underline{H}_3$).

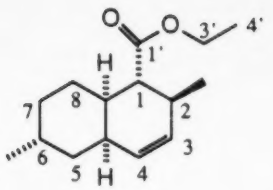


***N*-Acetylcysteamine (86).** A modification of the method of Schwab and Klassen was followed.[106b] A solution of diacetate **86a** (3.04 g, 18.9 mmol) in H_2O (57 mL) at 0 °C was treated with solid KOH (3.38 g, 60.2 mmol) over 15 min. The mixture was stirred under argon for 2 h at room temperature, then brought to pH 7 with 2 N HCl and saturated with NaCl. The mixture was extracted with CH_2Cl_2 (5 x 40 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give **86** (2.27 g, 99%), which was used without purification: IR ($CHCl_3$ cast) 3288 (br), 1652 (s), 1549 (s), 1373

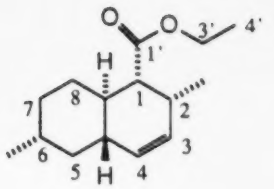
(m), 1280 (m); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.90 (br s, 1 H, NH), 3.43 (dt, 2 H, *J* = 6.4, 5.9 Hz, CH_2NH), 2.68 (ddt, 2 H, *J* = 8.3, 6.4, 1.9 Hz, SCH_2), 2.02 (s, 3 H, $COCH_3$), 1.36 (t, 1H, *J* = 8.3 Hz, SH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.52 (CO), 42.42 (CH_2NH), 24.10 (SCH_2), 22.81 ($COCH_3$); MS (EI) calcd for C_4H_9NOS 119.0405, found 119.0402 (M).



***N,S*-Diacetyl-β-mercaptoethylamine (86a).** The procedure of Gerstein and Jencks was used.[106a] A solution of 2-mercaptoethylamine hydrochloride (56.8 g, 500 mmol) in H_2O (150 mL) at -5 °C was treated with acetic anhydride (153 g, 150 mmol) and aqueous 8M KOH simultaneously over 110 min in such a way that the pH was maintained at 8. The mixture was then stirred for 1 h at room temperature and extracted with Et_2O (3 x 200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless liquid, which was distilled at reduced pressure to give pure **86a** (63.5 g, 79%): bp 137-141 °C (0.5 mm Hg); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.40 (br s, 1 H, NH), 3.40-3.36 (m, 2 H, CH_2NH), 3.02 (t, 2 H, *J* = 6.4 Hz, SCH_2), 2.33 (s, 3 H, CH_3COS), 1.97 (s, 3 H, $NHCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.50 (SCO), 170.26 (NCO), 39.38 (CH_2NH), 30.51, 29.01, 22.81 ($NC(O)CH_3$).



94



92

Ethyl (1*R*, 2*S*, 4a*R*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylate (94) and Ethyl (1*R*, 2*R*, 4a*S*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylate (92).

Procedure A. Thermal Reaction: The method of Roush and Gillis was adapted.[110] A solution of triene **83** (20.0 mg, 84.9 μmol) in dry toluene (1 mL) was placed in a thick-walled glass tube, and the solution was degassed with a stream of argon for 5 min. The tube was sealed under argon, then heated in an oil bath at 160 °C for 43 h. The tube was cooled, opened and the solvent was removed *in vacuo*. Flash chromatography (SiO_2; 3% Et_2O in pentane) of the clear residue yielded the *trans*-fused product **92** (7.5 mg, 38%, R_f 0.25), the *cis* fused product **94** (6.7 mg, 34%, R_f 0.21), and unreacted starting material (1.2 mg, 6%) as clear oils.

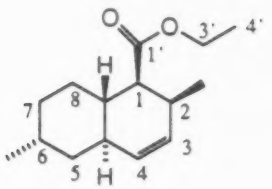
Data for the *trans*-fused product **92:** $[\alpha]_D^{20}$ -89.5° (*c* 1.40, $CHCl_3$); IR (CH_2Cl_2 cast) 3013 (m), 2951 (s), 2911 (s), 2873 (m), 2845 (m), 1737 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (ddd, 1H, *J* = 9.9, 4.0, 2.7 Hz, H-3), 5.38 (br d, 1H, *J* = 9.9 Hz, H-4), 4.13 (q, 2H, *J* = 7.1 Hz, H-3'), 2.55 (m, 1H, H-1), 2.53 (m, 1H, H-2), 1.95 (dddd, 1H, *J* = 12.0, 3.2, 3.0, 2.9 Hz, H-8eq), 1.77-1.68 (m, 3H, H-4a & H-7eq, & H-5eq), 1.52-1.43 (m , 1H, H-6), 1.35 (dddd, 1H, *J* = 12.0, 12.0, 12.0, 3.0 Hz, H-8a), 1.27 (t, 3H, *J* = 7.1 Hz, H-4'), 1.04 (dddd, 1H, *J* = 12.0, 12.0, 12.0, 3.0 Hz, H-8ax), 1.00-0.95 (m, 1H, H-7ax), 0.93 (d, 3H, *J* = 6.7 Hz, 2-C$\underline{H}_3$), 0.90 (d, 3H, *J* = 6.8 Hz, 6-C$\underline{H}_3$), 0.80 (ddd, 1H, *J* = 12.0, 12.0, 12.0 Hz, H-5ax); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.97 (C-1'), 130.93 & 130.92 (C$\underline{H}$=C$\underline{H}$), 59.79 (C-3'), 49.51 (C-1), 41.89 (C-4a), 41.63 (C-5), 36.20 (C-8a), 35.27 (C-7), 33.10 (C-6), 32.46 (C-2), 29.94 (C-8), 22.53

(6-$\underline{C}H_3$), 17.75 (2-$\underline{C}H_3$), 14.40 (C-4'); MS (EI) calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1775 (M^+, 11), 191.1429 (7), 162.1406 (100); Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.20; H, 10.20.

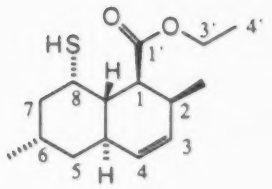
Data for the *cis*-fused product **94**: $[\alpha]_D^{20}$ +6.95° (*c* 0.81, $CHCl_3$); IR (CH_2Cl_2 cast) 3012 (m), 2958 (m), 2925 (m), 2871 (m), 1732 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (ddd, 1H, *J* = 10.0, 4.2, 2.4 Hz, H-3), 5.42 (ddd, 1H, *J* = 10.0, 1.6, 1.5 Hz, H-4), 4.17 (q, 1H, *J* = 7.1 Hz, 1 x H-3'), 4.16 (q, 1H, *J* = 7.07 Hz, 1 x H-3'), 2.52 (dqdd, 1H, *J* = 8.7, 6.1, 4.2, 1.6 Hz, H-2), 2.37 (dd, 1H, *J* = 10.0, 8.7 Hz, H-1), 2.29 (m, 1H, H-4a), 2.05 (m, 1H, H-8a), 1.94-1.83 (m , 1H, H-6), 1.74-1.64 (m, 2H, H-7eq & H-8eq), 1.48-1.35 (m, 2H, H-5eq & H-5ax), 1.38-1.29 (m, 1H, H-8ax), 1.28 (t, 3H, *J* = 7.1 Hz, H-4'), 1.18 (ddd, 1H, *J* = 9.7, 6.0, 5.0 Hz, H-7ax), 0.99 (d, 3H, *J* = 6.1 Hz, 2-$C\underline{H}_3$), 0.97 (d, 3H, *J* = 6.0 Hz, 6-$C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.22 (C-1'), 131.31 & 130.83 ($\underline{C}H=\underline{C}H$), 60.08 (C-3'), 47.92 (C-1), 36.31 (C-8a), 36.19 (C-5), 34.04 (C-2), 31.01 (C-4a), 28.06 (C-7), 27.41 (C-6), 24.03 (C-8), 20.61 (2-$\underline{C}H_3$), 18.66 (6-$\underline{C}H_3$), 14.43 (C-4'); MS (EI) calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1776 (M^+, 13), 162.1410 (100); Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.07; H, 10.01.

Procedure B. Lewis Acid Catalyzed Reaction: The procedure of Roush and Gillis was adapted.[110] Ethylaluminum dichloride (240 μL, 54.0 μmol, 1.8 M in toluene) was slowly added to a solution of triene ethyl ester **83** (13.4 mg, 56.8 μmol) in dry toluene (0.5 mL) and the mixture was stirred at room temperature for 3 h. The reaction mixture was then poured into 1N HCl (1.0 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 3% Et_2O in pentane) to yield the *trans*-fused product **92** (7.0 mg, 52%), the *cis*-fused product **94** (0.80 mg, 5.8%), and unreacted starting material **83** (1.3 mg, 10%), each with physical and spectral properties in good agreement with those

given in method A above.



93



142

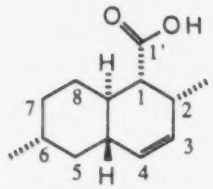
Ethyl (1*S*, 2*S*, 4a*R*, 6*R*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-1-carboxylate (93). Procedure A. A modification of the method of Gutierrez *et al.* was adopted.[133] Tributyltin hydride (0.5 mL, 1.86 mmol) and freshly recrystallized α,α'-azobis(isobutyronitrile) (AIBN, ~5 mg) were stirred with thioketal **141** (55.4 mg, 0.170 mmol) at 120 °C for 4 days. After cooling, the mixture was purified by flash chromatograghy (SiO_2; 2% Et_2O in pentane) to give the desired fully reduced product **93** (30.8 mg, 77%, R_f 0.20), and the mercapto-intermediate **142** (8.8 mg, 22%, R_f 0.16) as clear oils.

Data for **93:** $[\alpha]_D^{20}$ +143.3° (*c* 0.72, $CHCl_3$); IR (CH_2Cl_2 cast) 3012 (m), 2960 (s), 2912 (s), 2877 (m), 2850 (m), 1736 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (ddd, 1H, *J* = 9.9, 4.0, 3.0 Hz, H-3), 5.33 (br d, 1H, *J* = 9.9 Hz, H-4), 4.15 (q, 2H, *J* = 7.2 Hz, H-3'), 2.61-2.49 (m, 2H, H-1 & H-2), 2.10-2.00 (m, 1H, H-6), 1.93 (dddm, 1H, *J* = 12.8, 12.5, 2.6 Hz, H-4a), 1.72 (dddd, 1H, *J* = 12.5, 3.9, 3.9, 3.7 Hz, H-8eq), 1.63 (dddd, 1H, *J* = 13.2, 12.9, 3.9, 3.9 Hz, H-7ax), 1.56-1.53 (m, 1H, H-7eq), 1.53-1.48 (m, 1H, H-5eq), 1.45-1.35 (m, 1H, H-8a), 1.33 (ddd, 1H, *J* = 13.0,12.8, 4.8 Hz, H-5ax), 1.26 (t, 3H, *J* = 7.0 Hz, H-4'), 1.10 (dddd, 1H, *J* = 12.9, 12.9, 11.9, 3.7 Hz, H-8ax), 0.99 (d, 3H, *J* = 7.2 Hz, 6-C$\underline{H}_3$), 0.91 (d, 3H, *J* = 7.0 Hz, 2-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.88 (C-1'), 131.24 (<u>C</u>H=CH), 131.21 (<u>C</u>H=CH), 59.76 (C-3'), 49.60 (C-1), 38.73 (C-5), 37.20 (C-8a), 35.66 (C-4a), 32.35 (C-2), 31.94 (C-7), 27.63 (C-6), 24.49 (C-8), 18.37 (6-<u>C</u>H$_3$), 17.79 (2-<u>C</u>H$_3$), 14.40 (C-4'); MS (EI) calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1778 (M^+, 10), 191.1428 (7), 162.1410 (100); Anal.

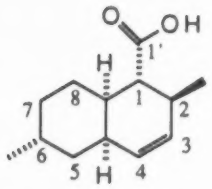
Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.50; H, 10.19.

Data for **142:** IR (CH_2Cl_2 cast) 3013 (w), 2960 (m), 2920 (m), 2875 (m), 2849 (m), 1730 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (ddd, 1H, *J* = 9.9, 4.5, 2.5 Hz, H-3), 5.48 (br d, 1H, *J* = 9.9 Hz, H-4), 4.17 (q, 2H, *J* = 7.1 Hz, H-3'), 3.87-3.78 (m, 1H, H-8eq), 2.89 (dd, 1H, *J* = 11.0, 6.6 Hz, H-1), 2.67-2.57 (m, 1H, H-2), 2.42 (br t, 1H, *J* = 12.5 Hz, H-4a), 2.20-2.10 (m, 1H, H-7eq), 2.10-2.00 (m, 1H, H-6), 1.86-1.75 (m, 1H, H-7ax), 1.75-1.70 (m, 1H, H-8ax), 1.52 (dm, 1H, *J* = 12.5 Hz, H-5eq), 1.35 (ddd, 1H, *J* = 12.5, 12.5, 5.2 Hz, H-5ax), 1.27 (t, 3H, *J* = 7.1 Hz, H-4'), 1.25 (br s, 1H, S-H), 1.20 (d, 3H, *J* = 7.1 Hz, 6-C$\underline{H}_3$), 0.92 (d, 3H, *J* = 7.1 Hz, 2-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.62 (C-1'), 130.98 ($\underline{C}$H=CH), 130.80 ($\underline{C}$H=CH), 60.09 (C-3'), 47.00 ($\underline{C}$H), 39.63 ($\underline{C}H_2$), 39.58 ($\underline{C}$H), 39.00 ($\underline{C}H_2$), 37.17 ($\underline{C}$H), 32.45 ($\underline{C}$H), 28.89 ($\underline{C}$H), 27.75 ($\underline{C}$H), 21.84 ($\underline{C}H_3$), 17.78 ($\underline{C}H_3$), 14.41 (C-4'); MS (CI, NH_3) 286 (MNH_4^+, 79), 269 (MH^+, 17).

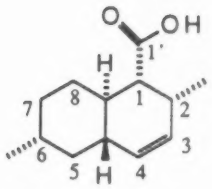
Procedure B. The procedure of Robins *et al.* was adopted.[126] Tributyltin hydride (0.014 mL, 0.051 mmol) and α,α'-azobis(isobutyronitrile) (1.8 mg, 0.07 mmol) were added to a solution of bis-thionocarbonate **128** (18.5 mg, 0.034 mmol) in dry toluene (1.0 mL). The reaction mixture was heated to 70-75 °C for 2.5 h, then to reflux for 4 h, at which time more tributyltin hydride (0.017 mL, 0.063 mmol) and toluene (1.0 mL) were added. The mixture was stirred overnight at 120 °C. The solvent was removed *in vacuo* and the residue was purified by flash chromatograghy (SiO_2; 2% Et_2O in pentane, R_f 0.20) to give **93** (0.6 mg, 8%) with similar spectral data as above.



(1*R*, 2*R*, 4a*S*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-1-carboxylic Acid (98). A modification of the method of Eisenbraun was adapted.[118] A solution of alcohol **102** (20.0 mg, 1.03 mmol) in acetone (1.5 mL) was slowly added to a cooled solution (0 °C) of chromium trioxide (40.8 mg, 0.408 mmol) in 1.5M H_2SO_4 (0.7 mL). The solution was stirred at room temperature for 2 h and concentrated *in vacuo* to produce an orange residue, which was purified by flash chromatography (SiO_2; 50% Et_2O in CH_2Cl_2, *Rf* 0.50) to yield **98** (11.0 mg, 51%) as a waxy solid: $[\alpha]_D^{20}$ -68.0° (*c* 0.10, CH_2Cl_2); IR (CH_2Cl_2 cast) 3600-2400 (br m), 3015 (m), 2871 (s), 2848 (s), 1705 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (ddd, 1H, *J* = 10.0, 4.1, 2.8 Hz, H-3), 5.39 (br d, 1H, *J* = 10.0 Hz, H-4), 2.65-2.50 (m, 2H, H-1 & H-2), 2.08-2.00 (m, 1H, H-8eq), 1.80-1.68 (m, 3H, H-4a & H-5eq & H-7eq), 1.54-1.42 (m , 1H, H-6), 1.42-1.28 (m, 1H, H-8a), 1.10-0.90 (m, 2H, H-7ax & H-8ax), 0.95 (d, 3H, *J* = 6.7 Hz, 2-C$\underline{H}_3$), 0.90 (d, 3H, *J* = 6.8 Hz, 6-C$\underline{H}_3$), 0.79 (ddd, 1H, *J* = 12.0, 12.0, 12.0 Hz, H-5ax); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.77 (C-1'), 130.92 & 130.62 (C$\underline{H}$=C$\underline{H}$), 49.39 (C-1), 41.73 (C-4a), 41.56 (C-5), 35.96 (C-8a), 35.22 (C-7), 33.05 (C-6), 32.33 (C-2), 29.91 (C-8), 22.49 (6-$\underline{C}H_3$), 17.65 (2-$\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{22}O_2$ 208.1463, found 208.1469 (M^+, 26), 163.1488 (100); Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.96; H, 9.68. Found: C, 74.72; H, 9.41.



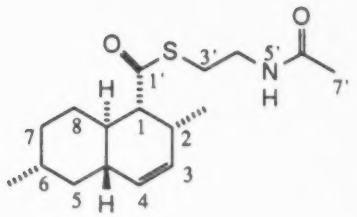
(2*S*,4a*R*) **99**



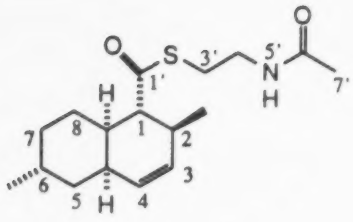
(2*R*,4a*S*) **98**

(1*R*, 2*S*, 4a*R*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-1-carboxylic Acid (99). The thermal Diels-Alder procedure for the formation of bicyclic ethyl ester **92** was used. Thus, cyclization of triene acid **85** (0.170 g, 0.815 mmol) afforded a 1:1 mixture of the *cis*- and *trans*-fused products, **98** and **99** (0.140 g, 83%), which was difficult to separate. Physical and spectral data were obtained for the mixture and the NMR assignments were made for (1*R*, **2*S***, **4a*R***, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylic acid **99** by comparing the mixture's NMR spectra with the NMR spectral data for the independently prepared pure stereoisomer of (1*R*, **2*R***, **4a*S***, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylic acid **98**.

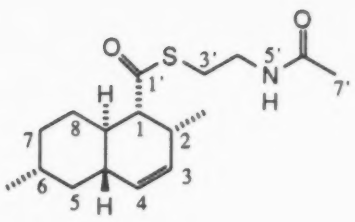
Data for **99**: IR (CH_2Cl_2 cast) 3600-2400 (br m), 3014 (m), 2956 (s), 2912 (s), 2872 (s), 2678 (m), 1704 (s), 1654 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (ddd, 1H, *J* = 10.0, 4.1, 2.8 Hz, H-3), 5.44 (ddd, 1H, *J* = 10.0, 2.0, 2.0 Hz, H-4), 2.58-2.50 (m, 1H, H-2), 2.39 (dd, 1H, *J* = 9.5, 8.0 Hz, H-1), 2.37-2.29 (m, 1H, H-4a), 2.11-2.05 (m, 1H, H-8a), 1.89-1.80 (m, 1H, H-6), 1.75-1.65 (m, 2H, H-7eq & H-8eq), 1.48-1.35 (m, 2H, H-5eq & H-5ax), 1.30-1.25 (m, 1H, H-8ax), 1.20.1.11 (m, 1H, H-7ax), 1.04 (d, 3H, *J* = 6.2 Hz, 2-C$\underline{H}_3$), 0.98 (d, 3H, *J* = 6.1 Hz, 6-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.89 (C-1'), 131.17 & 130.46 (C$\underline{H}$=C$\underline{H}$), 48.05 (C-1), 36.43 (C-5), 36.05 (C-8a), 33.46 (C-2), 30.91 (C-4a), 28.63 (C-7), 27.34 (C-6), 24.37 (C-8), 20.74 (2-$\underline{C}H_3$), 18.94 (6-$\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{22}O_2$ 208.1463, found 208.1461 (M^+, 21), 163.1488 (100); Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.96; H, 9.68. Found: C, 74.85; H, 9.80.



(1*R*, 2*R*, 4a*S*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-1-carboxylic Acid, *N*-Acetylcysteamine Thioester (100). The same method as for the Lewis acid catalyzed preparation of bicyclic ethyl ester **92** was employed. Thus, cyclization of triene NAC thioester **50** (95.6 mg, 0.309 mmol) afforded **100** (76.3 mg, 80%): mp 94-95 °C; $[\alpha]_D^{20}$ -31.5° (*c* 0.41, CH_2Cl_2); IR (CH_2Cl_2 cast) 3550-3100 (br m), 3100-3000 (br w), 2947 (m), 2923 (m), 2870 (m), 1687 (s), 1657 (s), 1550 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (br s, 1H, H-5'), 5.53 (ddd, 1H, *J* = 10.0, 4.2, 2.7 Hz, H-3), 5.38 (br d, 1H, *J* = 10.0 Hz, H-4), 3.49-3.41 (m, 2H, H-4'), 3.03 (t, 2H, *J* = 6.3 Hz, H-3'), 2.85 (dd, 1H, *J* = 11.2, 5.8 Hz, H-1), 2.63-2.55 (m, 1H, H-2), 1.95 (s, 3H, H-7'), 1.83-1.65 (m, 4H, H-4a & H-5eq & H-7eq & H-8eq), 1.50-1.45 (m, 2H, H-6 & H8a), 1.09-0.90 (m, 2H, H-7ax & H-8ax), 0.89 (d, 3H, *J* = 6.6 Hz, 2-C$\underline{H}_3$), 0.88 (d, 3H, *J* = 7.1 Hz, 6-C$\underline{H}_3$), 0.78 (ddd, 1H, *J* = 12.0, 12.0, 12.0 Hz, H-5ax); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.00 (C-1'), 171.80 (C-6'), 130.92 & 130.62 (C$\underline{H}$=C$\underline{H}$), 58.62 (C-1), 42.07 (C-4a), 41.48 (C-5), 40.23 (C-4'), 36.81 (C-8a), 35.12 (C-7), 33.59 (C-2), 33.00 (C-6), 29.46 (C-8), 28.28 (C-3'), 23.28 (C-7'), 22.46 (6-$\underline{C}H_3$), 17.42 (2-$\underline{C}H_3$); MS (EI) calcd for $C_{17}H_{27}NO_2S$ 309.1763, found 309.1760 (M^+, 1.4), 190.1359 (24), 163.1487 (100); Anal. Calcd for $C_{17}H_{27}NO_2S$: C, 65.98; H, 8.79. Found: C, 65.70; H, 9.28.



(2*S*,4a*R*) **101**

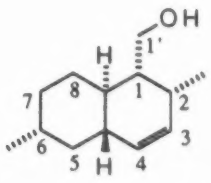


(2*R*,4a*S*) **100**

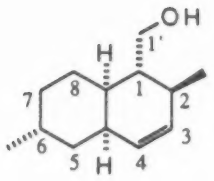
(1*R*, 2*S*, 4a*R*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-1-carboxylic Acid, *N*-Acetylcysteamine Thioester (101). The same thermal method as for the preparation of bicyclic ethyl ester **92** was employed. Thus, cyclization of triene NAC thioester **50** (21.3 mg, 68.8 μmol) afforded a 1:1 mixture of the *cis*- and *trans*-fused products, **100** and **101** (17.3 mg, 81%). Physical and spectral data were obtained for the mixture since the separation proved difficult and the NMR assignments were made for NAC (1*R*, **2*S***, **4a*R***, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylate **101** by comparing the mixture's NMR spectra with the NMR spectral data for the independently prepared pure stereoisomer of NAC (1*R*, **2*R***, **4a*S***, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylate **100**.

Data for **101**: IR (CH_2Cl_2 cast) 3550-3100 (br m), 3100-3000 (br w), 2926 (s), 2870 (m), 1683 (s), 1655 (s), 1553 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (br s, 1H, H-5'), 5.53 (ddd, 1H, *J* = 10.0, 4.2, 2.4 Hz, H-3), 5.43 (ddd, 1H, *J* = 10.0, 2.0, 2.0 Hz, H-4), 3.50-3.40 (m, 2H, H-4'), 3.06 (t, 1H, *J* = 6.4 Hz, H-3'), 2.62 (dd, 1H, *J* = 9.3, 8.4 Hz, H-1), 2.61-2.50 (m, 1H, H-2), 2.34-2.27 (m, 1H, H-4a), 2.13-2.07 (m, 1H, H-8a), 1.92-1.82 (m, 1H, H-6), 1.73-1.63 (m, 2H, H-7eq & H-8eq), 1.48-1.35 (m, 2H, H-5eq & H-5ax), 1.38-1.32 (m, 1H, H-8ax), 1.22-1.15 (m, 1H, H-7ax), 1.02 (d, 3H, *J* = 7.1 Hz, 2-$C\underline{H}_3$), 0.96 (d, 3H, *J* = 7.1 Hz, 6-$C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.42 (C-1'), 170.24 (C-6'), 131.26 & 130.62 ($\underline{C}H=\underline{C}H$), 56.55 (C-1), 40.22 (C-4'), 40.07 ($\underline{C}H_2$), 36.99 ($\underline{C}H$), 36.31($\underline{C}H_2$), 34.27 ($\underline{C}H$), 33.59 ($\underline{C}H$), 31.15 ($\underline{C}H$), 28.39

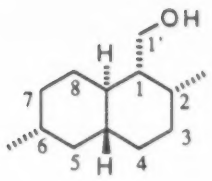
($\underline{C}H_2$), 28.28 (C-3'), 23.27 (C-7'), 22.46 ($\underline{C}H_3$), 20.61 ($\underline{C}H_3$); MS (EI) calcd for $C_{17}H_{27}NO_2S$ 309.1763, found 309.1760 (M^+, 1.7), 190.1355 (19), 163.1482 (100); MS (CI, NH_3) 327 (MNH_4^+, 21), 310 (MH^+, 100); Anal. Calcd for $C_{17}H_{27}NO_2S$: C, 65.98; H, 8.79. Found: C, 65.82; H, 8.95.



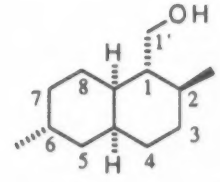
(1*R*, 2*R*, 4a*S*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethyl-1-hydroxymethylnaphthalene (102). The same method as for the preparation of alcohol **103** was employed. Thus, reduction of ethyl ester **92** (40.8 mg, 0.173 mmol) with $LiAlH_4$ (26.2 mg, 0.690 mmol) afforded **102** (26.9 mg, 80%): mp 64-65 °C; $[\alpha]_D^{20}$ +70.37° (*c* 0.054, CH_2Cl_2); IR (CH_2Cl_2 cast) 3600-3100 (br m), 3008 (m), 2949 (s), 2909 (s), 2869 (m), 1455 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (ddd, 1H, *J* = 9.7, 4.6, 2.7 Hz, H-3), 5.36 (br d, 1H, *J* = 9.7 Hz, H-4), 3.83 (dd, 1H, *J* = 10.7, 5.5 Hz, 1 x H-1'), 3.53 (dd, 1H, *J* = 10.7, 9.3 Hz, 1 x H-1'), 2.50-2.38 (m, 1H, H-2), 1.80-1.63 (m, 5H, H-1 & H-4a & H-5eq & H-7eq & H-8eq), 1.51-1.36 (m , 2H, OH & H-6), 1.11-0.92 (m, 3H, H-8a & H-7ax & H-8ax), 0.92 (d, 3H, *J* = 7.1 Hz, 2-$\underline{C}H_3$), 0.89 (d, 3H, *J* = 6.6 Hz, 6-$\underline{C}H_3$), 0.73 (ddd, 1H, *J* = 12.2, 12.2, 12.2 Hz, H-5ax); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 132.34 & 131.19 ($\underline{C}H$=$\underline{C}H$), 63.21 (C-1'), 44.13 (CH), 43.34 (CH), 41.83 (C-5), 37.34 (C-8a), 35.53 (C-7), 32.82 (C-6), 31.65 (C-2), 29.16 (C-8), 22.61 (6-$\underline{C}H_3$), 15.51 (2-$\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{22}O$ 194.1671, found 194.1669 (M^+, 10), 163.1487 (100); Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.15; H, 11.44.



(1*R*, 2*S*, 4a*R*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethyl-1-hydroxymethylnaphthalene (103). A modification of the procedure of VanMiddlesworth was used.[115] A solution of ethyl ester **94** (45.4 mg, 0.192 mmol) in dry Et_2O (0.7 mL) was added to a slurry of $LiAlH_4$ (29.2 mg, 7.68 mmol) in Et_2O (1.7 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was cooled to 0 °C and treated sequentially with H_2O (33 μL), 3M NaOH (33 μL), and H_2O (100 μL). The mixture was allowed to warm to room temperature and was stirred for an additional hour. $MgSO_4$ was added to the stirring solution and the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2; 30% Et_2O in pentane, R_f 0.35) to yield the desired alcohol **103** (32.0 mg, 86%) as a colourless solid: mp 59.5-60 °C; $[\alpha]_D^{20}$ +28.6° (*c* 0.028, CH_2Cl_2); IR (CH_2Cl_2 cast) 3600-3100 (br m), 3007 (m), 2946 (s), 2908 (s), 2869 (m), 1454 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50 (ddd, 1H, *J* = 10.1, 2.8, 2.8 Hz, H-3), 5.40 (ddd, 1H, *J* = 10.0, 2.0, 2.0 Hz, H-4), 3.58 (d, 2H, *J* = 6.8 Hz, H-1'), 2.35-2.28 (m, 1H, H-4a), 2.00-1.90 (m, 1H, H-2), 1.82-1.75 (m, 1H, H-8a), 1.69-1.57 (m, 3H, H-5eq & H-7eq & H-8eq), 1.57-1.42 (m, 2H, H-1 & H-6), 1.39-1.32 (m, 1H, H-8ax), 1.25-1.19 (m, 1H, H-5ax), 1.09 (d, 3H, *J* = 7.5 Hz, 2-C$\underline{H}_3$), 0.99-0.90 (m, 1H, H-7ax), 0.87 (d, 3H, *J* = 6.6 Hz, 6-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.60 & 129.80 (C$\underline{H}$=C$\underline{H}$), 65.51 (C-1'), 46.13 (C$\underline{H}$), 39.59 (C$\underline{H}_2$), 34.79 (C$\underline{H}$), 34.35 (C$\underline{H}_2$), 31.07 (C$\underline{H}$), 30.66 (C$\underline{H}$), 28.15 (C$\underline{H}$), 27.78 (C$\underline{H}_2$), 22.17 (C$\underline{H}_3$), 21.92 (C$\underline{H}_3$); MS (EI) calcd for $C_{13}H_{22}O$ 194.1671, found 194.1668 (M^+, 9), 163.1485 (100); Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.07; H, 11.52.

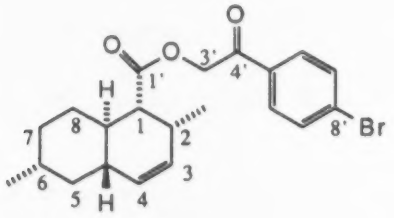


(1*R*, 2*R*, 4a*S*, 6*R*, 8a*R*)-2,6-Dimethyl-1-hydroxymethyldecalin (104). The same procedure as for the formation of decalin **105** was used. Thus, hydrogenation of alkene **102** (11.3 mg, 582 μmol) with Pd/C (10%, 4.62 mg) afforded **104** (7.4 mg, 65%): IR (CH_2Cl_2 cast) 3600-3100 (br m), 2946 (s), 2911 (s), 2854 (s), 1455 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (dd, 1H, *J* = 10.8, 5.1 Hz, 1 x H-1'), 3.45 (dd, 1H, *J* = 10.8, 9.1 Hz, 1 x H-1'), 2.15-2.07 (m, 1H), 1.77-1.66 (m, 2H), 1.61-1.50 (m, 3H), 1.45-1.15 (m, 6H), 1.10-0.90 (m, 3H), 0.89 (d, 3H, *J* = 7.2 Hz, $C\underline{H}_3$), 0.85 (d, 3H, *J* = 6.5 Hz, $C\underline{H}_3$), 0.68 (ddd, 1H, *J* = 11.9, 11.9, 11.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.15 (C-1'), 47.42 ($\underline{C}H$), 43.33 ($\underline{C}H$), 43.06 ($\underline{C}H_2$), 38.69 ($\underline{C}H$), 35.41 ($\underline{C}H_2$), 33.06 ($\underline{C}H_2$), 32.43 ($\underline{C}H$), 30.38 ($\underline{C}H_2$), 29.18 ($\underline{C}H$), 28.31 ($\underline{C}H_2$), 22.77 ($\underline{C}H_3$), 12.87 ($\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{24}O$ 196.1827, found 196.1826 (M^+, 3.4), 178.1721 (66), 165.1642 (41).



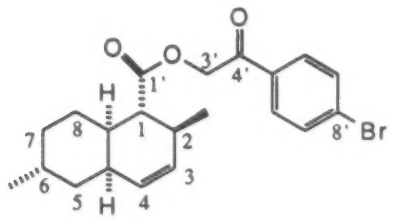
(1*R*, 2*S*, 4a*R*, 6*R*, 8a*R*)-2,6-Dimethyl-1-hydroxymethyldecalin (105). A modification of the procedure of Ernst and Wagner was adopted.[116] A slurry of alkene **103** (12.0 mg, 619 μmol) and Pd/C (10%, 1.76 mg) in EtOAc (1 mL) was shaken in a Parr shaker at 50 psi of H_2 for 18 h. The solution was filtered through Celite, the filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (SiO_2; 20% Et_2O in pentane) to give **105** (3.4 mg, 28%): IR (CH_2Cl_2 cast) 3600-3100 (br m), 2947 (s), 2908 (s), 2867 (s), 2845 (s), 1456 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)

δ 3.83 (dd, 1H, *J* = 12.0, 2.0 Hz, 1 x H-1'), 3.77 (dd, 1H, *J* = 12.0, 2.0 Hz, 1 x H-1'), 2.02-1.92 (m, 1H), 1.77-1.63 (m, 2H), 1.63-1.43 (m, 3H), 1.43-1.17 (m, 3H), 1.17-0.80 (m, 5H), 0.95 (d, 3H, *J* = 6.0 Hz, $C\underline{H}_3$), 0.86 (d, 3H, *J* = 6.2 Hz, $C\underline{H}_3$), 0.72-0.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.15 (C-1'), 47.42 ($\underline{C}H$), 43.33 ($\underline{C}H$), 43.06 ($\underline{C}H_2$), 38.69 ($\underline{C}H$), 35.41 ($\underline{C}H_2$), 33.06 ($\underline{C}H_2$), 32.43 ($\underline{C}H$), 30.38 ($\underline{C}H_2$), 29.18 ($\underline{C}H$), 28.31 ($\underline{C}H_2$), 22.77 ($\underline{C}H_3$), 12.87 ($\underline{C}H_3$); MS (EI) calcd for $C_{13}H_{24}O$ 196.1827, found 196.1826 (M^+, 5), 178.1721 (66), 165.1642 (50).

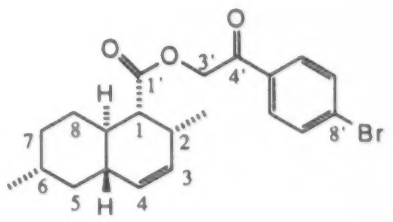


***p*-Bromophenacyl (1*R*, 2*R*, 4a*S*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-1-carboxylate (106).** The method of Shriner *et al.* was followed.[117] Aqueous 1N NaOH (20 μL) was added to a solution of acid **98** (9.4 mg, 45.1 μmol) in H_2O (0.5 mL), and the solution was then adjusted to pH 7 with 1N HCl. DMF (0.5 mL) and 2,4'-dibromoacetophenone were added to the solution, and the mixture was heated to reflux for 30 min. The mixture was poured into H_2O (1 mL) and Et_2O (2 mL), and the organic layer was washed with H_2O, and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by thin layer chromatography (SiO_2; 5% Et_2O in pentane, R_f 0.25) to yield **106** (7.3 mg, 40%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.61 (d, 2H, *J* = 8.5 Hz, Ar-H), 5.56 (ddd, 1H, *J* = 10.0, 4.1, 2.7 Hz, H-3), 5.39 (br d, 1H, *J* = 10.0 Hz, H-4), 5.31 (d, 1H, *J* = 16.4 Hz, 1 x H-3'), 5.23 (d, 1H, *J* = 16.4 Hz, 1 x H-3'), 2.75 (dd, 1H, *J* = 11.4, 6.0 Hz, H-1), 2.74-2.62 (m, 1H, H-2), 2.00-1.94 (m, 1H, H-8eq), 1.82-1.67 (m, 3H, H-4a & H-5eq & H-7eq), 1.62-1.50 (m , 1H, H-6), 1.50-1.38 (m, 1H, H-8a), 1.09-0.93 (m, 2H, H-7ax & H-8ax), 0.99 (d, 3H, *J* = 7.0 Hz, 2-$C\underline{H}_3$), 0.91 (d, 3H, *J* = 6.6 Hz, 6-$C\underline{H}_3$), 0.80 (ddd,

1H, J = 11.7, 11.7, 11.7 Hz, H-5ax); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 191.55 (C-4'), 175.57 (C-1'), 133.21 (C-5'), 132.34 (CH), 130.85 (CH), 130.11 (CH), 129.33 (CH), 129.08 (C-8'), 65.33 (C-3'), 49.29 (C-1), 41.96 (C-4a), 41.60 (C-5), 36.23 (C-8a), 35.26 (C-7), 33.10 (C-6), 32.52 (C-2), 29.81 (C-8), 22.53 (6-CH_3), 17.70 (2-CH_3); MS (CI, NH_3) 424 [MNH_4^+ (^{81}Br), 42], 422 [MNH_4^+ (^{79}Br), 43], 407 [MH^+ (^{81}Br), 0.8], 405 [MH^+ (^{79}Br), 0.8].



(2*S*,4a*R*) 107

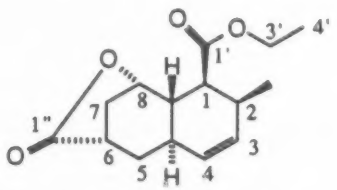


(2*R*,4a*S*) 106

p*-Bromophenacyl (1*R*, 2*S*, 4a*R*, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-1-carboxylate (107).** The same procedure as for the formation of ester **106** was used. Thus, a 1:1 mixture of acids **98** and **99** (76.1 mg, 0.365 mmol), afforded a 1:1 mixture of the *cis*- and *trans*-fused products, **106** and **107** (92.1 mg, 62%). Physical and spectral data were obtained for the mixture since the separation proved difficult and the NMR assignments were made for *p*-bromophenacyl (1*R*, **2*S, **4a*R***, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylate **107** by comparing the mixture's NMR spectra with the NMR spectral data for the independently prepared pure stereoisomer of *p*-bromophenacyl (1*R*, **2*R***, **4a*S***, 6*R*, 8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2,6-dimethylnaphthalen-1-carboxylate **106**.

Data for **107**: IR (CH_2Cl_2 cast) 3015 (w), 2949 (s), 2915 (s), 2870 (s), 1740 (s), 1706 (s), 1587 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 8.5 Hz, Ar-H), 7.61 (d, 2H, J = 8.5 Hz, Ar-H), 5.55 (ddd, 1H, J = 10.0, 4.1, 2.7 Hz, H-3), 5.44 (ddd, 1H, J = 10.0, 1.7, 1.6 Hz, H-4), 5.30 (s, 2H, H-3'), 2.62-2.55 (m, 1H, H-2), 2.55 (dd, 1H, J = 9.1, 8.3 Hz, H-1), 2.38-2.30 (m, 1H, H-4a), 2.16-1.99 (m, 1H, H-8a), 1.90-

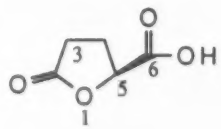
1.82 (m, 1H, H-6), 1.75-1.65 (m, 2H, H-7eq & H-8eq), 1.48-1.35 (m, 3H, H-5eq & H-5ax & H-8ax), 1.21-1.12 (m, 1H, H-7ax), 1.10 (d, 3H, J = 6.8 Hz, 2-C$\underline{H}_3$), 0.97 (d, 3H, J = 6.7 Hz, 6-C$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 191.65 (C-4'), 173.28 (C-1'), 133.05 (C-5'), 132.19 (C$\underline{H}$), 131.12 (C$\underline{H}$), 130.76 (C$\underline{H}$), 129.27 (C$\underline{H}$), 129.02 (C-8'), 65.56 (C-3'), 47.72 (C-1), 36.29 (C-5), 36.17 (C-8a), 33.92 (C-2), 30.86 (C-4a), 28.36 (C-7), 27.33 (C-6), 24.10 (C-8), 20.66 (2-C$\underline{H}_3$), 18.79 (6-C$\underline{H}_3$); MS (CI, NH_3) 424 [MNH_4^+ (^{81}Br), 97], 422 [MNH_4^+ (^{79}Br), 100], 407 [MH^+ (^{81}Br), 2.5], 405 [MH^+ (^{79}Br), 2.4]; Anal. Calcd for $C_{21}H_{25}BrO_3$: C, 62.23; H, 6.22. Found: C, 61.83; H, 6.22.



(+)-(1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1-(Ethoxycarbonyl)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-6,8-naphthalenecarbolactone (108).[119e] **Procedure A.**[119e] A 100 mL flask was washed with hexamethyldisilazane, dried at 120 °C overnight, and allowed to cool under argon. Dry mesitylene (30 mL), butylated hydroxytoluene (30.4 mg, 0.138 mmol), and the triene **117** (270 mg, 1.042 mmol) were placed in the flask, and the mixture was heated under reflux for 11 days. The vessel was cooled to room temperature and the solvent was evaporated *in vacuo*. The resulting oil was purified by chromatography (SiO_2; 1:1:8 CH_3CN : CH_2Cl_2 : toluene, R_f 0.37) to yield a clear oil. Recrystallization from Et_2O-petroleum ether gave **108** (133 mg, 48%) as white crystals: mp 60-62 °C (lit.[119e] mp 60-62 °C); $[\alpha]_D^{20}$ +260.5° (*c* 0.26, $CHCl_3$) (lit.[119e] $[\alpha]_D^{20}$ +260° (*c* 1.03, $CHCl_3$)); IR (CH_2Cl_2 cast) 2971 (m), 2929 (m), 1782 (s), 1729 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53-5.45 (m, 2H, C$\underline{H}$=C$\underline{H}$), 5.04 (d, 1H, J = 6.1 Hz, H-8eq), 4.16 (q, 2H, J = 7.1 Hz, H-3'), 2.85 (dd, 1H, J = 11.9, 6.6 Hz, H-1), 2.73-2.65 (m, 2H, H-6 & H-2), 2.48 (ddm, 1H, J = 12.0,

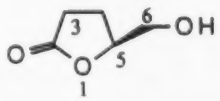
5.9 Hz, H-7eq), 2.40-2.25 (m, 1H, H-4a), 2.08-2.00 (m, 1H, H-5eq), 1.86 (d, 1H, J = 12.0 Hz, H-7ax), 1.73 (dd, 1H, J = 11.3 Hz, H-8a), 1.40 (ddd, 1H, J = 13.0, 13.0, 1.84 Hz, H-5ax), 1.27 (t, 3H, J = 7.1 Hz, H-4'), 0.88 (d, 3H, J = 7.1 Hz, 2-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.83 (C 1''), 173.03 (C-1'), 131.26 (C$\underline{H}$=CH), 128.07 (C$\underline{H}$=CH), 77.09 (C-8), 60.36 (C-3'), 46.05 (C-1), 39.29 (C-8a), 39.19 (C-6), 38.74 (C-7), 35.08 (C-4a), 32.65 (C-2), 31.80 (C-5), 17.28 (2-C$\underline{H}_3$), 14.28 (C-4'); MS (EI) calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1362 (M^+, 6), 218.0943 (9), 190.0994 (40), 145.1020 (100); Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.16; H, 7.77.

Procedure B. A modification of the procedure of Davidson *et al.* was used.[122] A 0.1-0.2 M solution of triene **117** in toluene was placed in a thick-walled glass tube, and was degassed for 5 min with argon. The tube was sealed and heated to 160 °C for 5 days. The solvent was removed and the resultant oil was purified as above to yield the cyclized product (60% yield) with identical spectral data to that isolated from procedure A.

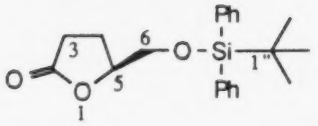


(+)-(5*S*)-(Carboxy)tetrahydrofuran-2-one (110).[120] A solution of sodium nitrite (126 g, 1.83 mol) in H_2O (270 mL) was added dropwise over 6 h to a mixture of (*S*)-(+)-glutamic acid (180 g, 1.22 mol) in H_2O (480 mL) and concentrated hydrochloric acid (252 mL) at 0 °C with vigorous stirring. The clear solution was stirred at room temperature overnight. Evaporation to dryness gave a pale yellow oil together with colourless crystals. EtOAc (600 mL) was added, the crystals were removed by filtration, and the filtrate was dried and concentrated *in vacuo*. Further evaporation of the solvent under high vacuum yielded a viscous yellow oil (160 g) which was used without further purification. A small portion (1.0 g) was recrystallized (EtOAc/petroleum ether) to yield

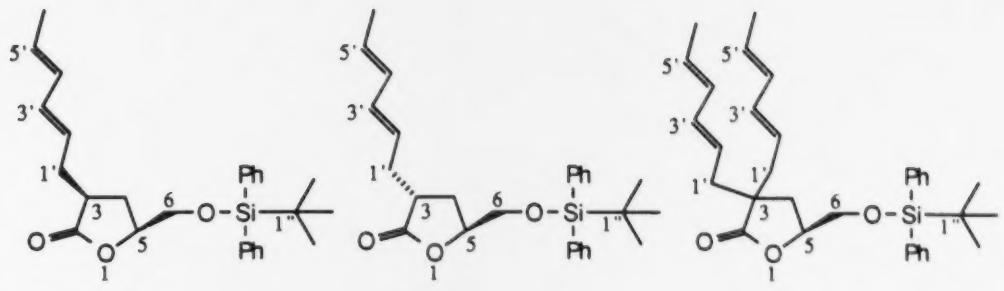
110 (0.520 g, 52%) as colourless prism-like crystals: mp 71-72 °C (lit.[120] mp 71-73 °C); $[\alpha]_D^{20}$ +12.5° (*c* 1.60, EtOH) (lit.[120] $[\alpha]_D^{20}$ +15.6° (*c* 2.0, EtOH)); IR (nujol) 1783 (s), 1724 (s), 1159 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (br s, 1H, COO<u>H</u>), 4.96-4.89 (m, 1H, H-5), 2.62-2.45 (m, 3H, H-3 & 1 x H-4), 2.37-2.27 (m, 1H, 1 x H-4); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.30 (C-2), 172.12 (C-6), 75.87 (C-5), 27.08 (<u>C</u>H_2), 25.79 (<u>C</u>H_2); MS (CI, NH_3) 148 (MNH_4^+, 100), 131 (MH^+, 1.3); Anal. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65. Found: C, 46.01; H, 4.56.



(+)-(5*S*)-(Hydroxymethyl)tetrahydrofuran-2-one (111).[120] A solution of acid **110** (85.0 g, 0.653 mol) in dry THF (400 mL) was treated dropwise with borane-methyl sulfide reagent (10.0 M, 77.0 mL, 0.770 mmol) at 0 °C. The solution was allowed to warm to room temperature and was stirred for 3 h. After cooling to 0 °C, the reaction was quenched by the slow addition of dry MeOH (200 mL). The solvent was removed *in vacuo* and the orange liquid was distilled [105-110 °C (0.2 mm Hg)] [lit.[120] bp 122-130 °C (0.6 mm Hg)] to yield a crude colourless oil (59.3 g), which was used without further purification. A small sample (1.0 g) was purified by flash chromatography (SiO_2; 10% EtOAc in Et_2O, R_f 0.20) to yield **111** (0.540 g, 54%) as a clear oil: $[\alpha]_D^{20}$ +38.5° (*c* 2.80, EtOH) (lit.[120] $[\alpha]_D^{20}$ +31.3° (*c* 2.92, EtOH)); IR (neat) 3400 (br s), 2941 (s), 2879 (m), 1771 (s), 1191 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65-4.55 (m, 1H, H-5), 3.83 (ddd, 1H, *J* = 12.6, 3.0, 3.0 Hz, 1 x H-6), 3.60 (dm, 1H, *J* = 12.6 Hz, 1 x H-6), 3.20 (br d, 1H, O<u>H</u>), 2.62-2.41 (m, 2H, H-3), 2.28-2.16 (m, 1H, 1 x H-4), 2.16-2.04 (m, 1H, 1 x H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.04 (C-2), 80.96 (C-5), 63.92 (C-6), 28.64 (<u>C</u>H_2), 23.08 (<u>C</u>H_2); MS (EI) calcd for $C_5H_8O_3$ 116.0473, found 116.0477 (M^+, 1.3); MS (CI, NH_3) 134 (MNH_4^+, 100), 117 (MH^+, 25); Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.89; H, 7.09.



(+)-(5*S*)-((*tert*-Butyldiphenylsiloxy)methyl)tetrahydrofuran-2-one (112).[119e] A solution of (+)-(5*S*)-(hydroxymethyl)tetrahydrofuran-2-one (**111**) (9.0 g, 0.078 mol), freshly-distilled pyridine (26.0 mL), and *tert*-butyldiphenylsilyl chloride (0.078 mol, 20.16 mL) in dry CH_2Cl_2 (110 mL) was stirred at room temperature for 20 h. The solution was washed with 2N HCl (2 x 90 mL), and brine (40 mL), then dried ($MgSO_4$), and evaporated *in vacuo*. The crude residue was recrystallized with Et_2O/petroleum ether to yield **112** (21.6 g, 79%) as colourless prisms: mp 75-77 °C (lit.[119e] mp 75-77 °C); $[\alpha]_D^{20}$ +33.9° (*c* 1.20, EtOH) (lit.[119e] $[\alpha]_D^{20}$ +35.5° (*c* 1.09, EtOH)); IR (CH_2Cl_2 cast) 3080 (w), 2957 (m), 2931 (m), 2858 (m), 1778 (s), 1113 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.63 (m, 4H, Ar-H), 7.40-7.36 (m, 6H, Ar-H), 3.87 (dd, 1H, *J* = 11.4, 3.3 Hz, 1 x H-6), 3.68 (dd, 1H, *J* = 11.4, 3.3 Hz, 1 x H-6), 2.72-2.62 (m, 1H, 1 x H-3), 2.55-2.45 (m, 1H, 1 x H-3), 2.33-2.17 (m, 2H, H-4), 1.05 (s, 9H, 1'-(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.47 (C-2), 135.66 (CH), 135.58 (CH), 132.98 (*ipso*-C), 132.60 (*ipso*-C), 129.94 (CH), 127.87 (CH), 79.98 (C-5), 65.50 (C-6), 28.58 (CH_2), 26.77 (1'-$C(CH_3)_3$), 23.66 (CH_2), 19.21 (C-1'); MS (CI, NH_3) 372 (MNH_4^+, 100), 355 (MH^+, 2.5); Anal. Calcd for $C_{21}H_{26}O_3Si$: C, 71.15; H, 7.39. Found: C, 71.33; H, 7.48.



3*S*,5*S* **113** 3*R*,5*S* **114** **115**

(+)-(3*S*,5*S*)-3-(2*E*,4*E*-Hexadienyl)-5-((*tert*-butyldiphenyl-siloxy)methyl)tetrahydrofuran-2-one (113).[119e] A solution of the protected lactone **112** (15.1 g, 42.6 mmol) in dry THF (200 mL) was added to a cooled (-78 °C), stirred solution of NaHMDS (1.0 M, 44.0 mmol) over 20 min. After the mixture was stirred for a further 15 min at -78 °C, freshly distilled 2*E*,4*E*-hexadienyl bromide (6.88 g, 42.8 mmol) in dry THF (40 mL) at -78 °C was rapidly added, and stirring was continued for 30 min. The cloudy mixture was then transferred *via* cannula into a cooled solution (-78 °C) of LHMDS (1.0 M, 46.0 mmol) and stirred for 30 min at -78 °C. Freshly distilled 2-bromo-2-methylpropane (5.90 g, 43.0 mmol) in cold (-78 °C) THF (40 mL) was added, and the reaction mixture was stirred at -78 °C for 30 min, and then quenched by the addition of saturated aqueous ammonium chloride (40 mL). The mixture was allowed to warm to room temperature, enough H_2O was added to dissolve all the solid, and the resulting two phases were poured into Et_2O (200 mL). The two layers were separated, and the organic phase was washed with saturated aqueous ammonium chloride (60 mL) and brine (60 mL). The combined aqueous solutions were extracted with Et_2O (200 mL), and the organic layer was washed with brine (100 mL). The combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo* to leave a crude orange oil (ca. 25 g). Flash chromatography (twice) (SiO_2; gradient elution 12:1 to 1:9 petroleum ether:EtOAc) yielded three products: the dialkylated product **115** (0.542 g, 3%, R_f 0.43); the 3*R*,5*S* anti-alkylated product **114** (2.49 g, 14%, R_f 0.28); and the desired 3*S*,5*S* syn-alkylated **113**

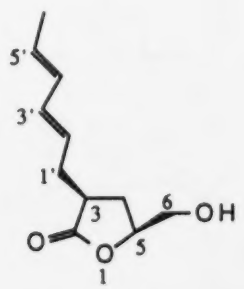
(10.4 g, 57%, R_f 0.17) as colourless oils. Due to an 8% impurity of the *E,Z*-isomer in the bromide used, each product contained its corresponding *E,Z*-isomer as a minor contaminant.

Data for the desired 3*S*,5*S* syn-alkylated **113:** $[\alpha]_D^{20}$ +42.9° (*c* 0.69, $CHCl_3$); IR (neat) 3018 (w), 2931 (m), 2857 (m), 1774 (s), 1589 (m), 1472 (m), 1114 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H, Ar-H), 7.48-7.36 (m, 6H, Ar-H), 6.06 (dd, 1H, *J* = 14.1, 10.4 Hz, H-3'), 5.98 (ddq, 1H, *J* = 14.2, 10.4, 1.6 Hz, H-4'), 5.63 (dq, 1H, *J* = 14.2, 6.6 Hz, H-5'), 5.47 (dt, 1H, *J* = 14.1, 6.9 Hz, H-2'), 4.52-4.42 (m, 1H, H-5), 3.88 (dd, 1H, *J* = 11.5, 3.4 Hz, 1 x H-6), 3.72 (dd, 1H, *J* = 11.5, 4.2 Hz, 1 x H-6), 2.80-2.60 (m, 1H, H-3 & 1 x H-1'), 2.20-2.35 (m, 2H, 1 x H-1' & 1 x H-4), 2.01-1.89 (m, 1H, 1 x H-4), 1.74 (d, 3H, *J* = 6.6 Hz, H-6'), 1.07 (s, 9H, 1"-(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.07 (C-2), 135.69 (CH), 135.61 (CH), 133.27 (CH), 133.13 (*ipso*-C), 132.86 (*ipso*-C), 131.14 (CH), 129.86 (CH), 128.50 (CH), 127.82 (CH), 126.78 (CH), 78.48 (C-5), 64.62 (C-6), 40.58 (C-3), 33.34 (CH_2), 29.27 (CH_2), 26.79 (1"-(CH_3)$_3$), 19.29 (C-1"), 18.02 (C-6'); MS (CI, NH_3) 452 (MNH_4^+, 100), 435 (MH^+, 7); Anal. Calcd for $C_{27}H_{34}O_3Si$: C, 74.61; H, 7.88. Found: C, 74.49; H, 8.15.

Data for the 3*R*,5*S* anti-alkylated product **114:** $[\alpha]_D^{20}$ +10.6° (*c* 1.11, $CHCl_3$); IR (neat) 3018 (w), 2957 (m), 2930 (m), 1774 (s), 1113 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.63 (m, 4H, Ar-H), 7.45-7.35 (m, 6H, Ar-H), 6.11 (dd, 1H, *J* = 14.1, 10.4 Hz, H-3'), 6.05 (ddq, 1H, *J* = 14.2, 10.4, 1.5 Hz, H-4'), 5.65 (dq, 1H, *J* = 14.2, 6.7 Hz, H-5'), 5.49 (dt, 1H, *J* = 14.1, 7.4 Hz, H-2'), 4.57-4.48 (m, 1H, H-5), 3.86 (dd, 1H, *J* = 11.4, 3.4 Hz, 1 x H-6), 3.66 (dd, 1H, *J* = 11.4, 3.2 Hz, 1 x H-6), 2.90 (dddd, 1H, *J* = 9.1, 9.0, 9.0, 4.4 Hz, H-3), 2.64-2.54 (m, 1H, 1 x H-1'), 2.32 (m, 2H, 1 x H-1' & 1 x H-4'), 2.10-1.98 (m, 1H, 1 x H-4'), 1.76 (d, 3H, *J* = 6.7 Hz, H-6'), 1.06 (s, 9H, 1"-(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.50 (C-2), 135.66 (CH), 135.55 (CH), 134.83 (CH), 133.43 (CH), 132.95 (*ipso*-C), 132.56 (*ipso*-C), 131.10 (CH), 129.95 (CH), 129.63 (CH), 128.63 (CH), 127.87 (CH), 127.71 (CH), 126.69 (CH), 78.01

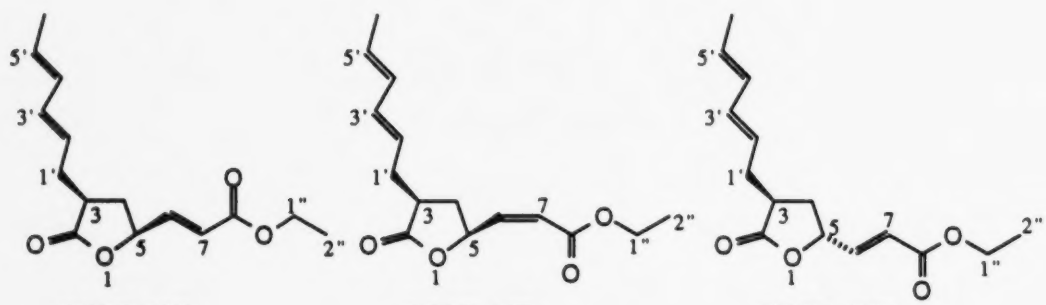
(C-5), 65.65 (C-6), 39.58 (C-3), 34.08 ($\underline{C}H_2$), 29.24 ($\underline{C}H_2$), 26.80 (1"-($\underline{C}H_3)_3$), 19.20 (C-1"), 18.04 (C-6'); MS (CI, NH_3) 452 (MNH_4^+, 83), 435 (MH^+, 9), 216 (100); Anal. Calcd for $C_{27}H_{34}O_3Si$: C, 74.61; H, 7.88. Found: C, 74.40; H, 8.04.

Data for the dialkylated product **115:** $[\alpha]_D^{20}$ +4.58° (*c* 5.56, $CHCl_3$); IR (neat) 3018 (w), 2958 (m), 2930 (m), 1769 (s), 1113 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H, Ar-$\underline{H}$), 7.48-7.36 (m, 6H, Ar-$\underline{H}$), 6.20-5.85 (m, 4H, 2 x H-3' & 2 x H-4'), 5.75-5.55 (m, 2H, 2 x H-5'), 5.55-5.35 (m, 2H, 2 x H-2'), 4.47-4.38 (m, 1H, H-5), 3.80 (dd, 1H, *J* = 11.4, 3.5 Hz, 1 x H-6), 3.64 (dd, 1H, *J* = 11.4, 4.6 Hz, 1 x H-6), 2.10-2.50 (m, 5H, 2 x H-1' & 1 x H-4), 2.01-1.92 (m, 1H, 1 x H-4), 1.74 (d, 3H, *J* = 7.2 Hz, H-6'), 1.72 (d, 3H, *J* = 6.9 Hz, H-6'), 1.05 (s, 9H, 1"-C($\underline{C}H_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.03 (C-2), 135.68 ($\underline{C}H$), 135.64 ($\underline{C}H$), 134.96 ($\underline{C}H$), 134.88 ($\underline{C}H$), 133.11 (*ipso*-$\underline{C}$), 133.00 (*ipso*-$\underline{C}$), 131.21 ($\underline{C}H$), 130.98 ($\underline{C}H$), 129.83 ($\underline{C}H$), 129.19 ($\underline{C}H$), 128.63 ($\underline{C}H$), 127.78 ($\underline{C}H$), 125.09 ($\underline{C}H$), 124.53 ($\underline{C}H$), 77.29 (C-5), 64.29 (C-6), 48.42 (C-3), 42.10 ($\underline{C}H_2$), 39.96 ($\underline{C}H_2$), 33.10 ($\underline{C}H_2$), 26.79 (1"-($\underline{C}H_3)_3$), 19.27 (C-1"); MS (CI, NH_3) 532 (MNH_4^+, 100), 515 (MH^+, 7); Anal. Calcd for $C_{33}H_{42}O_3Si$: C, 77.00; H, 8.22. Found: C, 76.78; H, 8.41.



(+)-(3*S*,5*S*)-3-(2*E*,4*E*-Hexadienyl)-5-(hydroxymethyl)tetrahydrofuran-2-one (116).[119e] Tetrabutylammonium fluoride (1.0 M, 8.30 mmol) was added to a solution of alkylated lactone **113** (3.24 g, 7.47 mmol) in THF (30 mL) at 0 °C. The orange solution was allowed to warm to room temperature and was stirred until the reaction was judged to be complete by TLC (ca. 1h). Et_2O (11 mL) was added and the solution

was washed with 3M citric acid (3 x 11 mL). The aqueous layers were back extracted with Et_2O (5 x 20 mL) and the combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo*. Flash chromatography of the resultant oil (SiO_2; 5% pentane in Et_2O, R_f 0.24) yielded crude **116** (1.38 g, 94%) as a colourless solid. A small portion was recrystallized from Et_2O-petroleum ether to give **116** as microprisms: mp 61-62 °C (lit.[119e] mp 62-63 °C); $[\alpha]_D^{20}$ +90.4° (*c* 0.48, MeOH) (lit.[119e] $[\alpha]_D^{20}$ +43° (*c* 0.043, MeOH)); IR (CH_2Cl_2 cast) 3284 (br m), 3271 (br m), 3120 (m), 2951 (m), 1756 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (dd, 1H, *J* = 14.1, 10.6 Hz, H-3'), 5.98 (ddq, 1H, *J* = 14.2, 10.6, 1.6 Hz, H-4'), 5.63 (dq, 1H, *J* = 14.2, 6.6 Hz, H-5'), 5.47 (dt, 1H, *J* = 14.1, 6.9 Hz, H-2'), 4.54-4.47 (m, 1H, H-5), 3.93 (dd, 1H, *J* = 11.5, 3.4 Hz, 1 x H-6), 3.63 (dd, 1H, *J* = 11.5, 4.5 Hz, 1 x H-6), 2.80-2.70 (m, 1H, H-3), 2.67-2.58 (m, 1H, 1 x H-1'), 2.34-2.22 (m, 2H, 1 x H-1' & 1 x H-4), 1.98 (br s, 1H, OH), 1.89-1.79 (m, 1H, 1 x H-4), 1.72 (d, 3H, *J* = 6.6 Hz, H-6'); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.36 (C-2), 133.24 (CH), 130.96 (CH), 128.60 (CH), 126.59 (CH), 79.09 (C-5), 63.66 (C-6), 40.69 (C-3), 33.13 (CH_2), 29.01 (CH_2), 17.95 (C-6'); MS (EI) calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1098 (M^+, 45), 165.0913 (11), 93.0699 (100); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.22; H, 8.46.



(3*S*,5*S*)-(6*E*) **117** (3*S*,5*S*)-(6*Z*) **119** (3*S*,5*R*)-(6*E*) **118**

(3*S*,5*S*)-5-[2-(Ethoxycarbonyl)-*E*-ethenyl]-3-(2*E*,4*E*-hexadienyl)tetrahydrofuran-2-one (117).[119e] Dry DMSO (1.52 mL, 21.5 mmol)

was added dropwise to a stirred and cooled (-78 °C) solution of distilled oxalyl chloride (0.80 mL, 9.12 mmol) in CH_2Cl_2 (9 mL). After 20 min, a solution of the alcohol **116** (1.28 g, 6.52 mmol) in THF (20 mL) was added slowly *via* cannula. After 30 min dry diisopropylethylamine (4.56 mL, 26.2 mmol) was slowly added to the already cloudy solution. The solution was stirred at -78°C for an additional 5 min and then the cooling bath was replaced by a salt/ice/H_2O bath. When the internal temperature reached ca. -10 °C, the cloudy solution was transferred *via* cannula to a stirred solution of (carbethoxymethylene)triphenylphosphorane (4.59 g, 13.2 mmol) in dry THF (17 mL), and the reaction mixture was stirred for 20 h at room temperature in the dark. The mixture was evaporated *in vacuo*, and the residual oil was taken up in EtOAc (100 mL) and washed with 2N HCl (2 x 30 mL). The combined aqueous layers were back extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 25% EtOAc in hexane) to give: (3*S*,5*S*)-5-[2-(ethoxycarbonyl)-*Z*-ethenyl]-3-(2*E*,4*E*-hexadienyl)tetrahydrofuran-2-one, (**119**) (86.2 mg, 5%, R_f 0.50); the epimerized (3*S*,5*R*)-5-[2-(ethoxycarbonyl)-*E*-ethenyl]-3-(2*E*,4*E*-hexadienyl)tetrahydrofuran-2-one (**118**) (0.172 g, 10%, R_f 0.37); and the desired *E*,*E*,*E*-triene **117** (1.17 g, 68%, R_f 0.33) as colourless oils.

If the starting alcohol was contaminated with any *E*,*Z*-isomer each product would contain its corresponding *E*,*Z*-isomer as a minor contaminant. The desired *E*,*E*,*E*-triene (1.17 g) could be isolated from any *E*,*Z*-diene olefin impurites using MPLC (silver stained silica gel, 2% EtOAc in CH_2Cl_2) followed by flash chromatograghy (SiO_2; gradient elution with 14:1 to 4:1 hexane-EtOAc) to yield a colourless oil (0.448 g, 26%). The initially isolated epimerized and *Z*-Wittig products were not further purified.

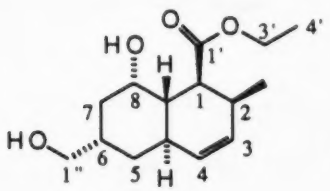
Data for desired *E*,*E*,*E*-triene **117**: $[\alpha]_D^{20}$ +107.0° (*c* 6.24, $CHCl_3$); IR (CH_2Cl_2 cast) 3019 (m), 2983 (m), 2935 (m), 2915 (m), 1779 (s), 1721 (s), 1685 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (dd, 1H, *J* = 15.7, 5.1 Hz, H-6), 6.10 (dd, 1H, *J* =

15.7, 1.6 Hz, H-7), 6.06 (ddt, 1H, *J* = 14.3, 10.4, 1.0 Hz, H-3'), 6.02 (ddq, 1H, *J* = 13.7, 10.4, 1.6 Hz, H-4'), 5.64 (dq, 1H, *J* = 13.7, 6.5 Hz, H-5'), 5.44 (dt, 1H, *J* = 14.3, 7.1 Hz, H-2'), 4.97-4.92 (m, 1H, H-5), 4.21 (q, 2H, *J* = 7.1 Hz, H-1"), 2.80-2.72 (m, 1H, H-3), 2.66-2.57 (m, 1H, 1 x H-1'), 2.57-2.51 (m, 1H, 1 x H-1'), 2.32-2.23 (m, 1H, 1 x H-4), 1.80-1.70 (m, 1H, 1 x H-4), 1.74 (d, 3H, *J* = 6.5 Hz, H-6'), 1.29 (t, 3H, *J* = 7.1 Hz, H-2"); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.14 (C-2), 165.69 (C-8), 143.40 (C-6), 133.73 (CH), 130.91 (CH), 129.05 (CH), 126.04 (CH) 122.33 (C-7), 76.21(C-5), 60.84 (C-1"), 40.62 (C-3), 34.20 (CH_2), 33.06 (CH_2), 18.06 (C-6'), 14.21 (C-2"); MS (EI) calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1361 (M^+, 3.7), 218.1307 (3.3), 138.0686 (45), 93.0706 (100); Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.20; H, 7.77.

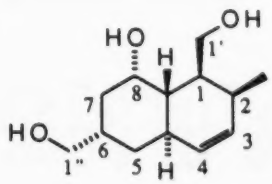
Data for the epimerized product **118:** IR (CH_2Cl_2 cast) 3019 (m), 2983 (m), 2960 (m), 2938 (m), 2914 (m), 1780 (s), 1721 (s), 1662 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (dd, 1H, *J* = 15.7, 4.4 Hz, H-6), 6.10-5.90 (m, 3H, H-3' & H-4' & H-7), 5.62 (dq, 1H, *J* = 13.7, 6.8 Hz, H-5'), 5.44 (dt, 1H, *J* = 14.3, 7.1 Hz, H-2'), 5.11-5.04 (m, 1H, H-5), 4.18 (q, 2H, *J* = 7.1 Hz, H-1"), 2.71-2.62 (m, 1H, H-3), 2.58-2.51 (m, 1H, 1 x H-1'), 2.33-2.15 (m, 3H, 1 x H-1' & H-4), 1.72 (d, 3H, *J* = 6.8 Hz, H-6'), 1.27 (t, 3H, *J* = 7.1 Hz, H-2"); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.59 (C-2), 165.47 (C-8), 143.95 (C-6), 133.73 (CH), 130.76 (CH), 128.96 (CH), 125.78 (CH), 121.78 (C-7), 75.56 (C-5), 60.66 (C-1"), 38.08 (C-3), 32.39 (CH_2), 32.43 (CH_2), 17.90 (C-6'), 14.05 (C-2"); MS (EI) calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1361 (M^+, 9), 138.0677 (50), 93.0703 (100); Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.25; H, 7.63.

Data for the *Z*-Wittig product **119:** IR (CH_2Cl_2 cast) 2984 (m), 2935 (m), 2914 (m), 1779 (s), 1717 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, 1H, *J* = 11.5, 7.0 Hz, H-6), 6.10-5.93 (m, 2H, H-3' & H-4'), 5.86 (dd, 1H, *J* = 11.5, 1.5 Hz, H-7), 5.85-5.80 (m, 1H, H-5), 5.62 (dq, 1H, *J* = 13.7, 6.6 Hz, H-5'), 5.44 (dt, 1H, *J* = 14.3,

7.1 Hz, H-2'), 4.17 (q, 2H, *J* = 6.9 Hz, H-1"), 2.84-2.67 (m, 2H, 1 x H-1' & H-3), 2.67-2.58 (m, 1H, 1 x H-1'), 2.31-2.20 (m, 1H, 1 x H-4), 1.72 (d, 3H, *J* = 6.6 Hz, H-6'), 1.70-1.50 (m, 1H, 1 x H-4), 1.28 (t, 3H, *J* = 6.9 Hz, H-2"); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.78 (C-2), 165.31 (C-8), 146.70 (C-6), 133.34 (CH), 130.89 (CH), 128.67 (CH), 126.31 (CH), 121.09 (C-7), 75.34 (C-5), 60.57 (C-1"), 40.50 (C-3), 33.85 (CH_2), 32.83 (CH_2), 17.93 (C-6'), 14.07 (C-2"); MS (EI) calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1354 (M^+, 29), 145.1018 (17), 93.0704 (100); Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.14; H, 7.69.



121



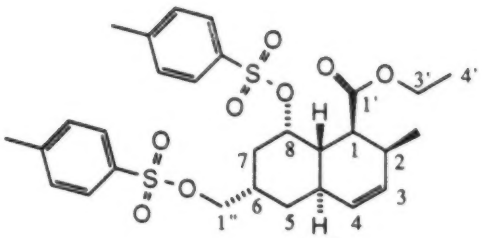
122

Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-6-hydroxymethyl-2-methylnaphthalene-1-carboxylate (121). A modification of the method of Blackwell *et al.* was adopted.[119e] A solution of the lactone **108** (0.476 g, 1.80 mmol) in dry THF (20 mL) was cooled to 0 °C, and lithium triethylborohydride ($LiBEt_3H$; 1.0 M in THF, 2.34 mmol) was added slowly (15 min). Further portions of lithium triethylborohydride (1.26 mmol) were added to react with intermediates generated, but the additions were limited so as to not fully reduce the starting material (TLC monitoring). H_2O (0.5 mL) was carefully added to destroy excess reagent, followed by 2N NaOH(aq) (1 mL) and 30% H_2O_2 solution (1 mL) dropwise. The resulting cloudy mixture was stirred vigorously for 1 h at room temperature, then poured into Et_2O (100 mL). The organic layer was washed with brine (20 mL) and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (SiO_2; 10% pentane in Et_2O) of

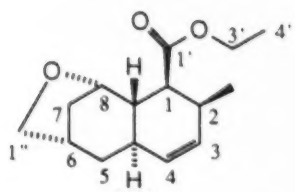
the resultant oil yielded two products: the desired product **121** (312 mg, 65%, R_f 0.20); and the triol **122** (9.88 mg, 20%, R_f 0.07) as a colourless solids.

Data for diol **121:** mp 100-100.5 °C; $[\alpha]_D^{20}$ +142.0° (*c* 0.29, $CHCl_3$); IR (CH_2Cl_2 cast) 3350 (br m), 3010 (m), 2965 (m), 2925 (s), 1732 (s), 1712 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (ddd, 1H, *J* = 9.8, 4.2, 2.8 Hz, C<u>H</u>=CH), 5.39 (br d, 1H, *J* = 9.8 Hz, C<u>H</u>=CH), 4.24 (br d, 1H, *J* = 2.1 Hz, H-8eq), 4.20-4.10 (m, 2H, H-3'), 3.78-3.69 (m, 2H, C<u>H</u>$_2$OH), 3.30 (br s, 2H, 2 x O<u>H</u>), 2.82 (dd, 1H, *J* = 11.9, 6.6 Hz, H-1), 2.65-2.54 (m, 1H, H-2), 2.52-2.42 (m, 1H, H-4a), 2.01-1.95 (m, 1H, H-6), 1.95-1.83 (m, 2H, H-7), 1.83-1.75 (m, 1H, H-5eq), 1.47 (ddd, 1H, *J* = 11.4, 11.0, 1.7 Hz, H-8a), 1.35 (ddd, 1H, *J* = 13.4, 13.4, 6.1 Hz, H-5ax), 1.26 (t, 3H, *J* = 7.1 Hz, H-4'), 0.91 (d, 3H, *J* = 7.1 Hz, 2-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.91 (C-1'), 131.19 (<u>C</u>H=CH), 130.54 (<u>C</u>H=CH), 67.98 (C-1"), 65.69 (C-8), 60.00 (C-3'), 45.12 (C-1), 39.85 (C-8a), 35.73 (C-7), 35.04 (C-5), 33.99 (C-6), 32.46 (C-2), 30.52 (C-4a), 17.63 (2-<u>C</u>H$_3$), 14.31 (C-4'); MS (CI, NH_3) 286 (MNH_4^+, 10), 269 (MH^+, 100); Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.74; H, 9.36.

Data for triol **122:** mp 141-142 °C; $[\alpha]_D^{20}$ +145.6° (*c* 0.077, CH_3OH); IR (CH_2Cl_2 cast) 3313 (br m), 3271 (br m), 3263 (br m), 2941 (m), 2900 (m), 1018 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.49 (ddd, 1H, *J* = 9.8, 4.2, 2.8 Hz, C<u>H</u>=CH), 5.34 (br d, 1H, *J* = 9.8 Hz, C<u>H</u>=CH), 4.10 (br d, 1H, *J* = 1.9 Hz, H-8eq), 3.78-3.50 (m, 4H, H-1' & H-1"), 2.78 (br s, 2H, 2 x O<u>H</u>), 2.55-2.17 (m, 2H, H-2 & H-4a), 2.20-1.65 (m, 5H, H-1 & H-6 & H-7 & H-5eq), 1.40-1.05 (m, 2H, H-5ax & H-8a), 0.77 (d, 3H, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.86 (<u>C</u>H=CH), 131.76 (<u>C</u>H=CH), 67.30 (C-1"), 65.93 (C-8), 64.59 (C-1'), 42.62 (<u>C</u>H), 41.45 (<u>C</u>H), 34.87 (<u>C</u>H$_2$), 34.36 (<u>C</u>H$_2$), 34.06 (<u>C</u>H), 33.80 (<u>C</u>H), 32.44 (<u>C</u>H), 15.58 (2-<u>C</u>H$_3$); MS (CI, NH_3) 244 (MNH_4^+, 7), 227 (MH^+, 100); Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.62; H, 9.97.



123



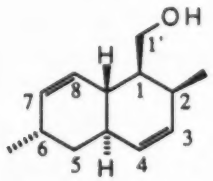
124

Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(4-toluenesulfonyl)oxy]-6-[[(4-toluenesulfonyl)oxy]-methyl]naphthalene-1-carboxylate (123). A modification of the method of Binkley was used.[123] Freshly recrystallized 4-toluenesulphonyl chloride (47.0 mg, 0.247 mmol) was added to a solution of alcohol **121** (30.4 mg, 0.113 mmol) and DMAP (1 crystal) in dry CH_2Cl_2. The mixture was strirred at room temperature for 2 days. The solvent was removed *in vacuo* and the residue was purified by flash chromatograghy (SiO_2; 50% Et_2O in pentane) to give the tricyclic ether **124** (16.1 mg, 25%, R_f 0.50) as an oil, and the desired product **123** (27.6 mg, 42%, R_f 0.25) as a viscous oil.

Data for **123:** IR (CH_2Cl_2 cast) 3055 (m), 2987 (m), 2966 (m), 2928 (m), 1726 (m), 1266 (s), 741 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77-7.68 (m, 4H, Ar-H), 7.38-7.28 (m, 4H, Ar-H), 5.53 (ddd, 1H, *J* = 9.9, 4.3, 2.7 Hz, CH=CH), 5.28 (br d, 1H, *J* = 1.9 Hz, H-8), 5.17 (d, 1H, *J* = 9.9 Hz, CH=CH), 4.21-4.05 (m, 3H, H-3' & 1 x H-1"), 3.80 (dd, 1H, *J* = 10.0, 4.9 Hz, 1 x H-1"), 2.71-2.53 (m, 2H, H-1 & H-2), 2.46 (s, 3H, Ar-CH_3), 2.44 (s, 3H, Ar-CH_3), 2.21-2.09 (m, 1H, H-4a), 2.00-1.85 (m, 1H, H-6), 1.80-1.50 (m, 4H, H-5eq & H-7 & H-8a), 1.28 (t, 3H, *J* = 7.1 Hz, H-4'), 1.22-1.09 (m, 1H, H-5ax), 0.83 (d, 3H, *J* = 6.9 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.56 (C-1'), 144.85 (*ipso*-C), 133.50 (*ipso*-C), 130.65 (CH), 130.05 (CH), 129.95 (CH), 129.91 (CH), 127.98 (CH), 127.80 (CH), 76.09 (C-8), 73.09 (CH_2), 59.59 (C-3'), 46.45 (CH), 42.30 (CH), 39.22 (CH_2), 35.85 (CH), 35.67 (CH_2), 34.65 (CH), 32.51 (CH), 21.73 (2 x Ar-CH_3), 17.86 (2-CH_3), 14.35 (C-4'); MS (CI, NH_3) 594

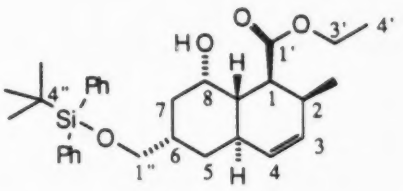
(MNH_4^+, 29), 577 (MH^+, 0.9), 507 (100).

Data for tricyclic ether **124:** $[\alpha]_D^{20}$ +212.8° (*c* 0.73, $CHCl_3$); IR (CH_2Cl_2 cast) 3025 (m), 2980 (s), 2930 (s), 2920 (s), 2870 (s), 1740 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.52-5.38 (m, 2H, C<u>H</u>=C<u>H</u>), 4.44 (d, 1H *J* = 6.2 Hz, H-8), 4.13 (q, 2H, *J* = 7.2 Hz, H-3'), 3.77 (br d, 2H, *J* = 1.9 Hz, H-1''), 2.82 (dd, 1H, *J* = 11.9, 6.6 Hz, H-1), 2.70-2.55 (m, 1H, H-2), 2.48-2.37 (m, 1H, H-4a), 2.37-2.22 (m, 1H, H-6), 2.04-1.91 (m, 1H, 1 x H-7), 1.77-1.60 (m, 3H, 1 x H-5 & 1 x H-7 & H-8a), 1.53-1.35 (m, 1H, 1 x H-5), 1.25 (t, 3H, *J* = 7.2 Hz, H-4'), 0.86 (d, 3H, *J* = 7.1 Hz, 2-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.56 (C-1'), 130.67 (<u>C</u>H=CH), 130.08 (<u>C</u>H=CH), 76.09 (C-8), 73.08 (C-6), 59.93 (C-3'), 46.50 (<u>C</u>H), 42.36 (<u>C</u>H), 39.24 (<u>C</u>H_2), 35.87 (<u>C</u>H), 35.70 (<u>C</u>H_2), 34.68 (<u>C</u>H), 32.52 (<u>C</u>H), 17.67 (2-<u>C</u>H_3), 14.35 (C-4'); MS (EI) calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1582 (M^+, 16), 159.1174 (100); Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.87; H, 9.02.



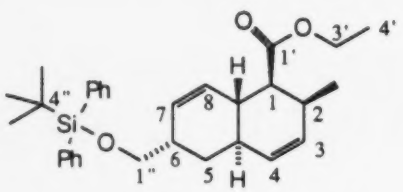
(1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,8a-Hexahydro-2,6-dimethyl-1-hydroxymethylnaphthalene (125). A modification of the procedure of Binkley was followed.[123] A solution of **123** (23.3 mg, 40.4 μmol) in THF (1 mL) was treated with $LiBEt_3H$ (1.0 M in THF; 0.12 mL, 0.121 mmol) and the reaction mixture was heated to reflux for 1 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 40% Et_2O in pentane, R_f 0.30) to give **125** (2.34 mg, 30%): IR (CH_2Cl_2 cast) 3390 (br m), 3010 (m), 2957 (s), 2924 (s), 2870 (s), 738 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.79 (br d, 1H, *J* = 10.0 Hz, C<u>H</u>=CH), 5.68-5.57 (m, 2H, C<u>H</u>=C<u>H</u>), 5.43 (br d, 1H, *J* = 10.0 Hz, C<u>H</u>=CH), 3.97 (dd, 1H, *J* = 10.4, 5.0 Hz,

1 x H-1'), 3.70 (dd, 1H, J = 10.4, 8.0 Hz, 1 x H-1'), 2.55-2.45 (m, 1H), 2.40-2.30 (m, 1H), 2.08-2.00 (m, 1H), 1.90-1.80 (m, 1H), 1.70-1.38 (m, 4H), 1.03 (d, 3H, J = 7.0 Hz, C$\underline{H}_3$), 0.94 (d, 3H, J = 6.9 Hz, C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.40 (C$\underline{H}$), 133.12 (C$\underline{H}$), 131.07 (C$\underline{H}$), 126.82 (C$\underline{H}$), 63.26 (C-1'), 43.52 (C$\underline{H}$), 36.93 (C$\underline{H}$), 36.19, 35.73 (C$\underline{H}$), 32.71 (C$\underline{H}$), 29.92 (C$\underline{H}$), 21.68 (C$\underline{H}_3$), 15.52 (C$\underline{H}_3$); MS (CI, NH_3) 210 (MNH_4^+, 45), 192 (MH^+, 17).



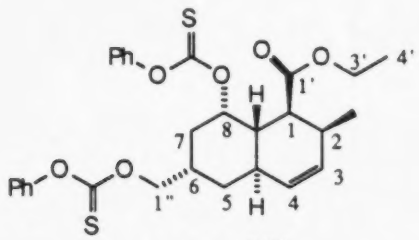
Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-6-(*t*-butyldiphenylsiloxymethyl)-8-hydroxy-2-methylnaphthalene-1-carboxylate (126). A modification of the method of Blackwell *et al.* was used.[119e] Dry pyridine (0.25 mL) and *tert*-butyldiphenylsilyl chloride (0.136 mL, 0.524 mmol) were added to a solution of diol **121** (54.8 mg, 204 μmol) in dry CH_2Cl_2 (1 mL). After stirring for 15 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 2N HCl (2 x 7 mL) and brine (7 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 x 15 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 10% Et_2O in pentane) to yield **126** (0.162 g, 61%) as a thick oil: IR (CH_2Cl_2 cast) 3580 (br m), 3520 (br m), 3050 (m), 2857 (s), 1731 (s), 1717 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.63 (m, 4H, Ar-$\underline{H}$), 7.47-7.36 (m, 6H, Ar-$\underline{H}$), 5.57 (ddd, 1H, J = 9.8, 4.2, 2.8 Hz, C$\underline{H}$=CH), 5.38 (br d, 1H, J = 9.8 Hz, C$\underline{H}$=CH), 4.24 (br d, 1H, J = 1.9 Hz, H-8), 4.21-4.09 (m, 2H, H-3'), 3.82 (dd, 1H, J = 10.2, 6.1 Hz, 1 x H-1"), 3.73 (dd, 1H, J = 10.2, 5.3 Hz, 1 x H-1"), 2.85 (dd, 1H, J = 11.9, 6.6 Hz, H-1), 2.68-2.58 (m, 2H, H-2 & H-4a), 2.50-2.40 (m, 1H), 1.98 (m, 1H), 1.94-1.83 (m, 2H), 1.75 (br d, 1H, J = 13.4 Hz), 1.50 (br t,

1H, J = 11.6 Hz), 1.33-1.28 (m, 1H), 1.27 (t, 3H, J = 7.1 Hz, H-4'), 1.06 (s, 9H, 4"-($C\underline{H}_3$)$_3$), 0.92 (d, 3H, J = 7.0 Hz, 2-$C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.79 (C-1'), 135.74 (<u>C</u>H), 135.68 (<u>C</u>H), 133.33 (*ipso*-C), 133.22 (*ipso*-C), 131.08 (<u>C</u>H), 130.79 (<u>C</u>H), 129.77 (<u>C</u>H), 129.74 (<u>C</u>H), 127.75 (<u>C</u>H), 68.60 (C-1"), 66.04 (C-8), 59.90 (C-3'), 45.00 (<u>C</u>H), 39.96 (<u>C</u>H), 35.54 (<u>C</u>H$_2$), 34.38 (<u>C</u>H$_2$), 34.34 (<u>C</u>H), 32.47 (<u>C</u>H), 29.80 (<u>C</u>H), 26.93 (4"-(<u>C</u>H$_3$)$_3$), 19.21 (C-4"), 17.67 (2-<u>C</u>H$_3$), 14.32 (C-4'); MS (CI, NH_3) 524 (MNH_4^+, 4.6), 507 (MH^+, 100).

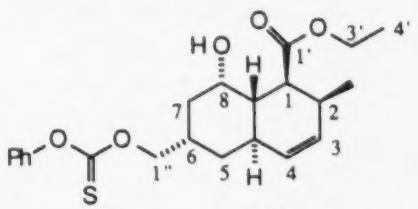


Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,8a-Hexahydro-6-(*t*-butyldiphenylsiloxymethyl)-2-methylnaphthalene-1-carboxylate (127). A modification of the procedure of Tipson was adopted.[124] A solution of **126** (30.6 mg, 60.4 μmol) in dry pyridine (2 mL) was treated with phosphorus oxychloride (56.3 μL, 0.603 mmol). The reaction mixture was stirred for 1 h at room temperature, and then partitioned between Et_2O (20 mL) and H_2O (10 mL). The aqueous layer was extracted with Et_2O (10 mL) and the combined organic fractions were washed with 2N HCl (10 mL), H_2O (10 mL), and brine (10 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 30% Et_2O in pentane, R_f 0.70) to yield **127** (12.8 mg, 42%) as a viscous oil: IR (CH_2Cl_2 cast) 3015 (m), 2998 (m), 2961 (s), 2931 (s), 1735 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71-7.61 (m, 4H, Ar-<u>H</u>), 7.45-7.30 (m, 6H, Ar-<u>H</u>), 5.77 (br d, 1H, J = 10.0 Hz, C<u>H</u>=CH), 5.62-5.52 (m, 2H, C<u>H</u>=C<u>H</u>), 5.44 (br d, 1H, J = 11.2 Hz, C<u>H</u>=CH), 4.17 (q, 2H, J = 7.1 Hz, H-3'), 3.59 (dd, 1H, J = 10.8, 9.3 Hz, 1 x H-1"), 3.47 (dd, 1H, J = 10.8, 6.0 Hz, 1 x H-1"), 2.75-2.40 (m, 3H), 2.23-2.07 (m, 1H), 1.97-1.70 (m, 2H), 1.62-1.49 (m, 1H), 1.28 (t, 3H, J

= 7.1 Hz, H-4'), 1.05 (s, 9H, 4"-($\underline{C}H_3)_3$), 0.91 (d, 3H, J = 7.0 Hz, 2-$\underline{C}H_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.61 (C-1'), 135.66 ($\underline{C}H$), 133.91 (*ipso*-C), 131.56 ($\underline{C}H$), 131.34 ($\underline{C}H$), 130.60 ($\underline{C}H$), 129.63 ($\underline{C}H$), 127.67 ($\underline{C}H$), 66.77 (C-1"), 60.00 (C-3'), 48.48 ($\underline{C}H$), 38.12 ($\underline{C}H$), 35.57 ($\underline{C}H$), 34.85 ($\underline{C}H$), 32.83, 30.62 ($\underline{C}H_2$), 26.93 (4"-($\underline{C}H_3)_3$), 19.34 (C-4"), 17.50 (2-$\underline{C}H_3$), 14.40 (C-4'); MS (CI, NH_3) 506 (MNH_4^+, 100), 489 (MH^+, 10).



128



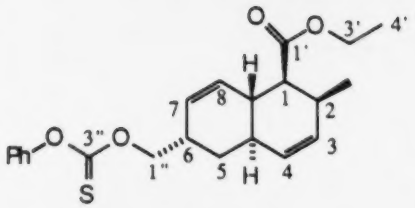
129

Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(phenoxythiocarbonyl)oxy]-6-[[(phenoxythiocarbonyl)oxy]-methyl]-naphthalene-1-carboxylate (128). The method of Robins *et al.* was used.[126] Dry pyridine (0.2 mL, 2.41 mmol) and phenyl chlorothionocarbonate (PTC-Cl, 0.084 mL, 0.603 mmol) were added to a stirred solution of diol **121** (162 mg, 0.603 mmol) in dry CH_2Cl_2 (4 mL). After 2 h, DMAP (30.9 mg) was added to the orange slurry. After 1 h, more PTC-Cl (0.02 mL) was added and the solution was stirred overnight. More PTC-Cl was added (0.064 mL) and after 5 h the reaction mixture was quenched with Et_2O (10 mL) and H_2O (5 mL). The organic layer was washed with 1 M HCl (5 mL) and brine (5 mL). The combined aqueous layers were back-extracted once with Et_2O (10 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatograghy (SiO_2; 50% Et_2O in pentane) to give the bis-thionocarbonate **128** (34.1 mg, 11%, R_f 0.70), and the primary thionocarbonate **129** (169 mg, 69%, R_f 0.50) as oils.

Data for bis-thionocarbonate **128:** $[\alpha]_D^{20}$ +156.6° (*c* 0.25, $CHCl_3$); IR (CH_2Cl_2 cast)

2965 (m), 2927 (m), 1762 (m), 1729 (s), 1592 (m), 1490 (s), 1279 (s), 1202 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.21 (m, 6H, Ar-H), 7.20-7.05 (m, 4H, Ar-H), 5.86 (br d, 1H, *J* = 2.3 Hz, H-8), 5.64 (ddd, 1H, *J* = 9.8, 4.5, 2.6 Hz, CH=CH), 5.43 (br d, 1H, *J* = 9.8 Hz, CH=CH), 4.67 (dd, 1H, *J* = 10.8, 9.3 Hz, 1 x H-1"), 4.58 (dd, 1H, *J* = 10.8, 6.0 Hz, 1 x H-1"), 4.25-4.10 (m, 2H, H-3'), 2.85 (dd, 1H, *J* = 11.6, 5.9 Hz, H-1), 2.75-2.60 (m, 1H, H-2), 2.60-2.35 (m, 3H, H-4a & H-6 & 1 x H-7), 2.10-1.73 (m, 3H, H-5eq & 1 x H-7 & H-8a), 1.48 (ddd, 1H, *J* = 13.7, 13.6, 5.3 Hz, H-5ax), 1.29 (t, 3H, *J* = 7.2 Hz, H-4'), 0.96 (d, 3H, *J* = 7.0 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.01 (OCSO), 193.73 (OCSO), 172.92 (C-1'), 153.42 (*ipso*-C), 153.28 (*ipso*-C), 131.53 (CH), 129.64 (CH), 129.57 (CH), 129.52 (CH), 126.60 (CH), 126.55 (CH), 122.04 (CH), 80.88 (C-8), 70.94 (C-1"), 60.52 (C-3'), 44.85 (CH), 39.34 (CH), 32.65 (CH_2), 32.35 (CH), 31.22 (CH), 30.20 (CH), 29.99 (CH_2), 17.56 (2-CH_3), 14.47 (C-4'); MS (EI) calcd for $C_{29}H_{32}O_6S_2$ 540.1640 found 540.1652 (M^+, 0.2), 495.1300 (0.5); MS (CI, NH_3) 558 (MNH_4^+, 0.2), 541 (MH^+, 0.8).

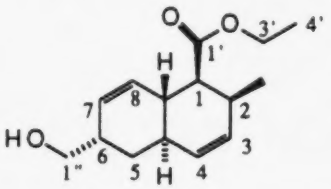
Data for primary thionocarbonate **129:** IR (CH_2Cl_2 cast) 3520 (br m), 2966 (m), 2927 (m), 1729 (s), 1712 (s), 1201 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47-7.36 (m, 2H, Ar-H), 7.33-7.24 (m, 1H, Ar-H), 7.15-7.08 (m, 2H, Ar-H), 5.60 (ddd, 1H, *J* = 9.8, 4.5, 2.6 Hz, CH=CH), 5.42 (br d, 1H, *J* = 9.8 Hz, CH=CH), 4.85 (dd, 1H, *J* = 10.8, 9.3 Hz, 1 x H-1"), 4.69 (dd, 1H, *J* = 10.8, 6.0 Hz, 1 x H-1"), 4.34 (br d, 1H, *J* = 2.4 Hz, H-8), 4.16 (q, 1H, *J* = 7.2 Hz, 1 x H-3'), 4.14 (q, 1H, *J* = 7.2 Hz, 1 x H-3'), 2.87 (dd, 1H, *J* = 11.6, 5.9 Hz, H-1), 2.70-2.30 (m, 3H, H-2 & H-4a & H-6), 2.00-1.80 (m, 3H, H-7 & OH), 1.65-1.50 (m, 2H, H-5eq & H-8a), 1.45-1.30 (m, 1H, H-5ax), 1.27 (t, 3H, *J* = 7.2 Hz, H-4'), 0.95 (d, 3H, *J* = 7.0 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.21 (OCSO), 173.69 (C-1'), 153.45 (*ipso*-C), 131.21 (CH), 130.62 (CH), 129.53 (CH), 126.52 (CH), 122.03 (CH), 77.52 (C-1"), 66.56 (C-8), 60.06 (C-3'), 45.00 (CH), 40.06 (CH), 34.87 (CH_2), 33.32 (CH_2), 32.44 (CH), 31.80 (CH), 28.98 (CH), 17.55 (2-CH_3), 14.34 (C-4'); MS (CI, NH_3) 422 (MNH_4^+, 3.5), 405 (MH^+, 100).



Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,8a-Hexahydro-2-methyl-6-[[(phenoxythiocarbonyl)oxy]methyl]-naphthalene-1-carboxylate (130). A solution of monothionocarbonate **129** (96.8 mg, 0.239 mmol), dry pyridine (0.292 mL, 3.61 mmol), phenyl chlorothionocarbonate (PTC-Cl, 0.399 mL, 2.89 mmol), and DMAP (30 mg) in DMF (3 mL) was stirred at room temperature for 4 days. The reaction mixture was quenched with Et_2O (30 mL) and H_2O (10 mL). The organic layer was washed with 1M HCl (2 x 25 mL) and brine (25 mL). The combined aqueous layers were back-extracted once with Et_2O (20 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatograghy (SiO_2; 50% Et_2O in pentane) to give the elimination product **130** (53.0 mg, 27%, R_f 0.65), and starting material **129** (0.108 g, 56%, R_f 0.45) as oils. Physical and spectral properties of the mono-protected product were similiar to those previously mentioned.

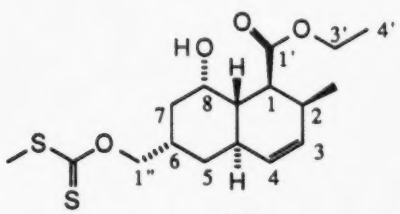
Data for elimination product **130:** $[\alpha]_D^{20}$ +49.5° (*c* 0.20, $CHCl_3$); IR (CH_2Cl_2 cast) 3013 (m), 2967 (m), 2928 (m), 2870 (m), 1782 (m), 1732 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.38 (m, 2H, Ar-H), 7.35-7.25 (m, 1H, Ar-H), 7-16-7.09 (m, 2H, Ar-H), 5.93 (br d, 1H, *J* = 10.1 Hz, CH=CH), 5.66-5.57 (m, 2H, CH=CH), 5.48 (br d, 1H, *J* = 9.9 Hz, CH=CH), 4.47 (dd, 1H, *J* = 10.7, 5.5 Hz, 1 x H-1"), 4.36 (dd, 1H, *J* = 10.7, 8.6 Hz, 1 x H-1"), 4.19 (q, 2H, *J* = 7.1 Hz, H-3'), 2.87-2.76 (m, 1H), 2.75-2.59 (m, 2H), 2.22 (br t, 1H, *J* = 10.0 Hz), 1.98 (br t, 1H, *J* = 10.4 Hz), 1.88 (br d, 1H, *J* = 13.7 Hz), 1.65 (ddd, 1H, *J* = 13.6, 13.6, 6.9 Hz), 1.27 (t, 3H, *J* = 7.1 Hz, H-4'), 0.93 (d, 3H, *J* = 6.9 Hz, 2-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.19 (C-3"), 173.37

(C-1'), 153.40 (*ipso*-C), 133.18 (CH), 132.06 (CH), 129.88 (CH), 129.56 (CH), 126.89 (CH), 126.59 (CH), 121.96 (CH), 76.48 (C-1"), 60.11 (C-3'), 48.20 (CH), 35.41 (CH), 34.65 (CH), 34.54 (CH), 32.80 (CH), 30.95 (C-5), 17.42 (2-CH_3), 14.40 (C-4'); MS (CI, NH_3) 404 (MNH_4^+, 26), 387 (MH^+, 3.6), 233 (100).

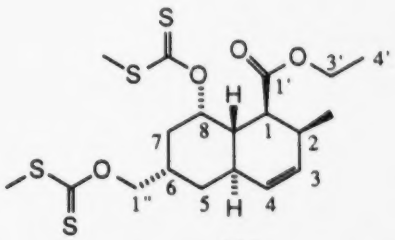


Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,8a-Hexahydro-6-(hydroxymethyl)-2-methylnaphthalene-1-carboxylate (131). A modification of the procedure of Barton *et al.* was used.[127] A solution of tributyltin hydride (0.141 mL, 0.523 mmol) and α,α'-azobis(isobutyronitrile) (3.0 mg, 0.18 mmol) in dry toluene (5 mL) was slowly added to a refluxing solution of bis-thionocarbonate **128** (47.2 mg, 0.87 mmol) in toluene (10 mL) over 1 h. The mixture was allowed to stir overnight at 120 °C. The solvent was removed *in vacuo* and the oil was purified by flash chromatography (SiO_2; 40% Et_2O in pentane, R_f 0.30) to yield **131** (20.5 mg, 94%) as a clear colourless solid: mp 65-67 °C; $[\alpha]_D^{20}$ +114.0° (*c* 0.04, $CHCl_3$); IR (CH_2Cl_2 cast) 3300 (br m), 3016 (m), 2967 (s), 2928 (s), 2916 (s), 2817 (s), 1733 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (br d, 1H, *J* = 10.1 Hz, CH=CH), 5.62-5.53 (m, 2H, CH=CH), 5.47 (br d, 1H, *J* = 9.9 Hz, CH=CH), 4.18 (q, 2H, *J* = 7.2 Hz, H-3'), 3.59 (dd, 1H, *J* = 10.5, 5.3 Hz, 1 x H-1"), 3.48 (dd, 1H, *J* = 10.5, 7.9 Hz, 1 x H-1"), 2.71-2.58 (m, 2H), 2.47-2.37 (m, 1H), 2.32-2.12 (m, 1H), 2.00-1.80 (m, 2H), 1.62-1.50 (m, 2H), 1.27 (t, 3H, *J* = 7.2 Hz, H-4'), 0.91 (d, 3H, *J* = 7.0 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.56 (C-1'), 132.24 (CH=CH), 131.71 (CH=CH), 130.35 (CH=CH), 128.45 (CH=CH), 66.22 (C-1"), 60.05 (C-3'), 48.39 (CH), 38.20 (CH), 35.44 (CH), 35.04 (CH), 32.79 (CH), 30.92 (CH_2), 17.44 (2-CH_3), 14.38 (C-4'); MS

(EI) calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1563 (M^+, 6), 219.1387 (11), 145.1015 (100); Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.63; H, 8.98.



132



133

Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-2-methyl-6-[[[(methylthio)thiocarbonyl]oxy]methyl]naphthalene-1-carboxylate (132). Procedure A. A modification of the method of Fuller and Stick was used.[128] Sodium hydride (17.4 mg, 0.435 mmol) was added to a solution of diol **121** (53.0 mg, 0.198 mmol) and one crystal of imidazole in THF (2 mL). After 30 min the reaction was treated with distilled carbon disulfide (0.071 mL, 0.119 mmol) (rapid addition) and after an additional 30 min with methyl iodide (0.043 mL, 0.692 mmol). The solution was stirred for a further 30 min and then glacial acetic acid (0.027 mL) was added slowly. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and H_2O (5 mL). The organic layer was washed with 1 M HCl (5 mL) and brine (5 mL). The combined aqueous layers were back-extracted once with CH_2Cl_2 (10 mL) and the combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 10% Et_2O in pentane) to yield the bis-dithiocarbonate **133** (17.9 mg, 20%, R_f 0.30), and the mono-dithiocarbonate **132** (36.7 mg, 41%, R_f 0.05) as colourless oils.

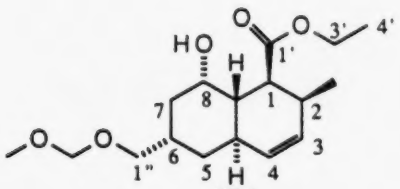
Data for **132:** $[\alpha]_D^{20}$ +162.9° (*c* 0.42, $CHCl_3$); IR (CH_2Cl_2 cast) 3500 (br m), 3015 (m), 2967 (m), 2921 (m), 1731 (s), 1714 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (ddd, 1H, *J* = 9.8, 4.6, 2.6 Hz, C<u>H</u>=CH), 5.39 (br d, 1H, *J* = 9.8 Hz, C<u>H</u>=CH), 4.90 (dd, 1H, *J* = 10.9, 9.3 Hz, 1 x H-1"), 4.76 (dd, 1H, *J* = 10.9, 6.1 Hz, 1 x H-1"), 4.31

(dd, 1H, *J* = 2.6, 2.5 Hz, H-8), 4.21-4.09 (m, 2H, H-3'), 2.85 (dd, 1H, *J* = 11.6, 5.9 Hz, H-1), 2.66-2.59 (m, 1H, H-2), 2.56 (s, 3H, SC<u>H</u>$_3$), 2.51-2.41 (m, 1H, H-4a), 2.41-2.33 (m, 1H, H-6), 1.92-1.76 (m, 2H, H-7), 1.60-1.50 (m, 2H, H-5eq & H-8a), 1.33 (ddd, 1H, *J* = 13.4, 13.4, 5.1 Hz, H-5ax), 1.26 (t, 3H, *J* = 7.1 Hz, H-4'), 0.92 (d, 3H, *J* = 7.1 Hz, 2-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.94 (S<u>C</u>SO), 173.69 (C-1'), 131.14 (<u>C</u>H=CH), 130.66 (<u>C</u>H=CH), 77.18 (C-1"), 66.52 (C-8), 60.04 (C-3'), 44.99 (<u>C</u>H), 40.02 (<u>C</u>H), 34.86 (<u>C</u>H$_2$), 33.42 (<u>C</u>H$_2$), 32.48 (<u>C</u>H), 31.88 (<u>C</u>H), 28.98 (<u>C</u>H), 18.96 (S<u>C</u>H$_3$), 17.54 (2-<u>C</u>H$_3$), 14.33 (C-4'); MS (CI, NH_3) 376 (MNH_4^+, 10), 359 (MH^+, 6), 268 (100); Anal. Calcd for $C_{17}H_{26}O_4S_2$: C, 56.95; H, 7.31. Found: C, 57.16; H, 7.52.

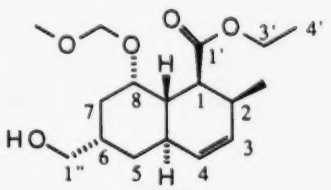
Data for **133:** IR (CH_2Cl_2 cast) 2967 (m), 2921 (m), 2873 (m), 2856 (m), 1730 (m), 1648 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, 1H, *J* = 2.6, 2.5 Hz, H-8), 5.62 (ddd, 1H, *J* = 9.8, 4.6, 2.6 Hz, C<u>H</u>=CH), 5.42 (br d, 1H, *J* = 9.8 Hz, C<u>H</u>=CH), 4.82 (dd, 1H, *J* = 10.9, 9.3 Hz, 1 x H-1"), 4.46 (dd, 1H, *J* = 10.9, 6.7 Hz, 1 x H-1"), 4.16-4.03 (m, 2H, H-3'), 2.76 (dd, 1H, *J* = 11.5, 5.9 Hz, H-1), 2.67-2.60 (m, 1H, H-2), 2.54 (s, 3H, SC<u>H</u>$_3$), 2.53 (s, 3H, SC<u>H</u>$_3$), 2.53-2.40 (m, 2H, H-4a & H-6), 2.40-2.33 (m, 1H, 1 x H-7), 1.92-1.75 (m, 3H, H-5eq & 1 x H-7 & H-8a), 1.42 (ddd, 1H, *J* = 13.4, 13.4, 5.1 Hz, H-5ax), 1.25 (t, 3H, *J* = 7.1 Hz, H-4'), 0.93 (d, 3H, *J* = 7.1 Hz, 2-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.66 & 215.01 (2 x S<u>C</u>SO), 172.85 (C-1'), 131.60 (<u>C</u>H=CH), 129.79 (<u>C</u>H=CH), 79.68 (C-8), 75.94 (C-1"), 60.45 (C-3'), 44.94 (<u>C</u>H), 39.43 (<u>C</u>H), 32.67 (<u>C</u>H$_2$), 32.36 (<u>C</u>H), 31.24 (<u>C</u>H), 30.49 (<u>C</u>H), 30.35 (<u>C</u>H$_2$), 19.13 (S<u>C</u>H$_3$), 18.91 (S<u>C</u>H$_3$), 17.54 (2-<u>C</u>H$_3$), 14.31 (C-4'); MS (EI) calcd for $C_{19}H_{28}O_4S_4$ 448.0870, found 448.0858 (M^+, 0.14), 404.0530 (1.4), 307.1370 (13.0), 159.1174 (100).

Procedure B. A modification of the procedure of di Cesare and Gross was used.[130] A solution of tetrabutylammonium hydrogen sulfate (691 mg, 2.04 mmol) and diol **121** (497 mg, 1.85 mmol) in distilled benzene (15 mL) was treated (with vigorous

stirring), with 4N NaOH(aq) (15 mL), followed by a quick addition of carbon disulfide (0.23 mL, 3.70 mmol) and methyl iodide (0.173 mL, 2.78 mmol). After 10 min, ice (30 g) and Et_2O (30 mL) were added to quench the reaction. The aqueous layer was extracted with Et_2O (2 x 30 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The resultant pale orange oil was purified by flash chromatograghy (SiO_2; 30% Et_2O in pentane, R_f 0.30) to give **132** (564 mg, 85%) as a pale yellow oil having the same physical and spectral data as above.



134



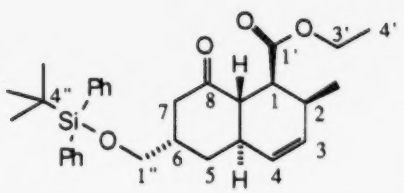
135

Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-8-hydroxy-6-(methoxymethoxymethyl)-2-methylnaphthalene-1-carboxylate (134). The method of Fried and coworkers was adopted.[168] The diol **121** (54.8 mg, 0.204 mmol) in dry THF (1 mL) was added to a slurry of NaH (60% dispersion in oil, 8.2 mg, 0.204 mmol) in THF (0.5 mL). After the evolution of gas was complete, the solution was cooled to 0 °C and chloromethyl methyl ether (0.016 mL, 0.204 mmol) was slowly added. The mixture was allowed to warm to room temperature, and was then treated with diisopropylethylamine (0.071 mL, 0.409 mmol) and chloromethyl methyl ether (0.016 mL, 0.204 mmol) to drive the reaction to completion. The solvent was removed *in vacuo* and flash chromatography (SiO_2; 50% pentane in Et_2O) of the resultant oil yielded three products: the desired **134** (34.1 mg, 54%, R_f 0.20); **135** (7.1 mg, 11%, R_f 0.10); and unreacted diol (1.6 mg, 3%, R_f 0.02).

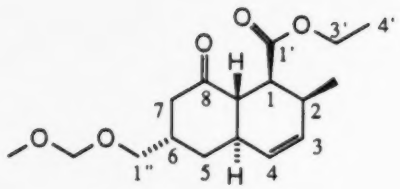
Data for **134:** IR (CH_2Cl_2 cast) 3486 (br m), 3014 (m), 2963 (s), 2929 (s), 2888 (s), 2853 (s), 1731 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (ddd, 1H, J = 9.8, 4.5, 2.6 Hz, C<u>H</u>=CH), 5.38 (br d, 1H, J = 9.8 Hz, C<u>H</u>=CH), 4.64 & 4.63 (ABq, 2H, J =

6.6 Hz, OCH_2O), 4.20 (br d 1H, *J* = 3.0 Hz, H-8), 4.21-4.09 (m, 2H, H-3'), 3.71 (dd, 1H, *J* = 9.6, 6.3 Hz, 1 x H-1"), 3.66 (dd, 1H, *J* = 9.6, 5.0 Hz, 1 x H-1"), 3.35 (s, 3H, OCH_3), 2.84 (dd, 1H, *J* = 11.9, 6.6 Hz, H-1), 2.66-2.55 (m, 1H, H-2), 2.45-2.32 (m, 1H, H-4a), 2.13-2.04 (m, 1H, H-6), 1.95-1.83 (m, 2H, H-7), 1.82-1.72 (m, 1H, H-5eq), 1.48 (ddd, 1H, *J* = 11.3, 11.3, 2.2 Hz, H-8a), 1.35 (ddd, 1H, *J* = 13.4, 13.4, 6.0 Hz, H-5ax), 1.25 (t, 3H, *J* = 7.1 Hz, H-4'), 0.90 (d, 3H, *J* = 7.1 Hz, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.74 (C-1'), 131.00 (CH=CH), 130.91 (CH=CH), 96.58 (OCH_2O), 72.86 (C-1"), 65.88 (C-8), 59.92 (C-3'), 55.47 (OCH_3), 45.06 (CH), 40.02 (CH), 35.37 (CH_2), 35.01 (CH_2), 32.42 (CH), 32.25 (CH), 29.90 (CH), 17.63 (2-CH_3), 14.33 (C-4'); MS (CI, NH_3) 330 (MNH_4^+, 6), 313 (MH^+, 100).

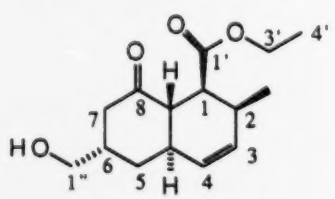
Data for **135:** IR (CH_2Cl_2 cast) 3486 (br m), 2962 (s), 2930 (s), 2911 (s), 2889 (s), 1731 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (ddd, 1H, *J* = 9.8, 4.5, 2.6 Hz, CH=CH), 5.40 (br d, 1H, *J* = 9.8 Hz, CH=CH), 4.64 (d, 1H, *J* = 6.3 Hz, 1 x OCH_2O), 4.47 (d, 1H, *J* = 6.3 Hz, 1 x OCH_2O), 4.20-4.05 (m, 2H), 3.79-3.65 (m, 2H, H-1"), 3.33 (s, 3H, OCH_3), 2.83 (dd, 1H, *J* = 11.9, 6.6 Hz, H-1), 2.65-2.55 (m, 1H, H-2), 2.49-2.33 (m, 1H, H-4a), 2.30-2.13 (m, 1H, H-6), 2.15-1.93 (m, 2H, H-7 & OH), 1.93-1.75 (m, 1H, H-5eq), 1.67 (ddd, 1H, *J* = 15.0, 6.0, 3.0 Hz, 1 x H-7), 1.55 (ddd, 1H, *J* = 10.8, 10.8, 2.2 Hz, H-8a), 1.33 (ddd, 1H, *J* = 12.6, 12.6, 6.0 Hz, H-5ax), 1.27 (t, 3H, *J* = 7.0 Hz, H-4'), 0.89 (d, 3H, *J* = 7.0 Hz, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.74 (C-1'), 131.14 (CH=CH), 130.61 (CH=CH), 96.73 (OCH_2O), 74.48 (C-8), 66.58 (C-1"), 59.90 (C-3'), 55.89 (OCH_3), 44.85 (CH), 39.63 (CH), 34.90 (CH), 33.90 (CH_2), 32.47 (CH), 31.86 (CH_2), 30.31 (CH), 17.66 (2-CH_3), 14.38 (C-4'); MS (CI, NH_3) 330 (MNH_4^+, 24), 313 (MH^+, 26), 281 (100).



Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-6-(*t*-butyldiphenylsiloxymethyl)-2-methylnaphthalen-8-one-1-carboxylate (136). The same procedure as for the preparation of ketone **137** was used. Thus, oxidation of alcohol **126** (63.0 mg, 0.124 mmol) with pyridinium dichromate (70.1 mg, 0.186 mmol) afforded **136** (56.6 mg, 90%) after purification by flash chromatography (SiO_2; 20% Et_2O in pentane, *Rf* 0.20): IR (CH_2Cl_2 cast) 2960 (s), 2930 (s), 2857 (s), 1735 (s), 1718 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65-7.59 (m, 4H, Ar-H), 7.45-7.35 (m, 6H, Ar-H), 5.63 (ddd, 1H, *J* = 9.8, 4.5, 2.6 Hz, CH=CH), 5.42 (ddd, 1H, *J* = 9.8, 1.6, 1.5 Hz, CH=CH), 4.22-4.09 (m, 2H, H-3'), 3.56 (dd, 1H, *J* = 10.4, 6.6 Hz, 1 x H-1"), 3.46 (dd, 1H, *J* = 10.4, 8.6 Hz, 1 x H-1"), 2.74 (dd, 1H, *J* = 11.5, 6.4 Hz, H-1), 2.71-2.58 (m, 3H), 2.58-2.49 (m, 1H), 2.32 (br d, 1H, *J* = 14.2 Hz), 2.15-2.05 (m, 2H), 1.66 (ddd, 1H, *J* = 12.9, 12.9, 4.9 Hz, H-5ax), 1.26 (t, 3H, *J* = 7.1 Hz, H-4'), 1.05 (s, 9H, 4"-(CH_3)$_3$), 0.89 (d, 3H, *J* = 7.1 Hz, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.89 (C-8), 173.68 (C-1'), 135.58 (CH), 133.55 (*ipso*-C), 133.48 (*ipso*-C), 131.97 (CH), 129.73 (CH), 128.71 (CH), 127.74 (CH), 65.08 (C-1"), 60.16 (C-3'), 49.27 (CH), 43.13 (CH_2), 42.73 (CH), 38.55 (CH), 37.70 (CH), 32.45 (CH_2), 31.23 (CH), 26.92 (4"-(CH_3)$_3$), 19.27 (C-4"), 17.78 (2-CH_3), 14.25 (C-4'); MS (CI, NH_3) 522 (MNH_4^+, 100), 505 (MH^+, 42).



Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-6-(methoxymethyloxymethyl)-2-methylnaphthalen-8-one-1-carboxylate (137). A modification of the procedure of Furber and Mander was used.[129] A solution of alcohol **134** (22.0 mg, 0.70 mmol) and pyridinium dichromate (39.7 mg, 0.106 mmol) in dry CH_2Cl_2 (1 mL) was stirred at room temperature for 36 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 50% Et_2O in pentane, R_f 0.25) to yield the desired keto-ester **137** (21.2 mg, 98%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.65 (ddd, 1H, *J* = 9.8, 4.3, 2.5 Hz, C<u>H</u>=CH), 5.45 (ddd, 1H, *J* = 9.8, 1.6, 1.5 Hz, C<u>H</u>=CH), 4.58 (s, 2H, OC<u>H</u>$_2$O), 4.15 (q, 2H, *J* = 7.2 Hz, H-3'), 3.40 (d, 2H, *J* = 7.2 Hz, H-1"), 3.33 (s, 3H, OC<u>H</u>$_3$), 2.87-2.52 (m, 5H), 2.37 (ddd, 1H, *J* = 13.0, 1.6, 1.6 Hz), 2.30-2.18 (m, 1H), 2.00 (ddt, 1H, *J* = 13.7, 1.7, 1.6 Hz), 1.73 (ddd, 1H, *J* = 13.3, 13.3, 5.0 Hz), 1.26 (t, 3H, *J* = 7.2 Hz, H-4'), 0.89 (d, 3H, *J* = 7.1 Hz, 2-C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.88 (C-8), 173.66 (C-1'), 132.25 (<u>C</u>H=CH), 128.55 (<u>C</u>H=CH), 96.57 (O<u>C</u>H$_2$O), 69.19 (C-1"), 60.25 (C-3'), 55.35 (O<u>C</u>H$_3$), 49.38 (<u>C</u>H), 43.41 (<u>C</u>H$_2$), 42.78 (<u>C</u>H), 38.14 (<u>C</u>H), 36.48 (<u>C</u>H), 33.26 (<u>C</u>H$_2$), 31.24 (<u>C</u>H), 17.79 (2-<u>C</u>H$_3$), 14.27 (C-4').



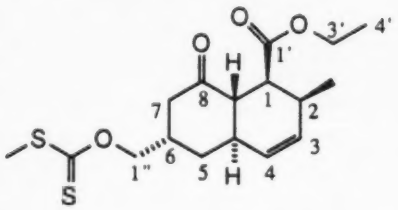
Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-6-(hydroxymethyl)-2-methylnaphthalen-8-one-1-carboxylate (138).

Procedure A. A modification of the method of Blackwell *et al.* was used.[119e] A

solution of silylated ketone **136** (50.0 mg, 0.099 mmol) in THF (0.5 mL) was treated with tetrabutylammonium fluoride (1.0M in THF, 0.11 mL, 0.11 mmol), and the reaction mixture was stirred overnight at room temperature. The solution was diluted with Et_2O (20 mL) and washed with 3M citric acid (3 x 10 mL) and H_2O (10 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 75% Et_2O in petroleum ether, R_f 0.25) to afford **138** (27.3 mg, 91%) as an oil: IR (CH_2Cl_2 cast) 3440 (br m), 2966 (m), 2927 (m), 1733 (s), 1714 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (ddd, 1H, *J* = 9.8, 4.5, 2.6 Hz, C<u>H</u>=CH), 5.46 (ddd, 1H, *J* = 9.8, 1.6, 1.5 Hz, C<u>H</u>=CH), 4.22-4.09 (m, 2H, H-3'), 3.56 (dd, 1H, *J* = 10.9, 7.2 Hz, 1 x H-1"), 3.52 (dd, 1H, *J* = 10.9, 7.7 Hz, 1 x H-1"), 2.81 (dd, 1H, *J* = 11.5, 6.4 Hz, H-1), 2.73 (dd, 1H, *J* = 13.6, 7.2 Hz), 2.72-2.60 (m, 2H), 2.53-2.45 (m, 1H), 2.36 (ddd, 1H, *J* = 13.5, 1.2, 1.2 Hz), 2.32-2.23 (m, 1H), 2.02 (dm, 1H, *J* = 13.9 Hz), 1.72 (ddd, 1H, *J* = 12.9, 12.9, 4.9 Hz), 1.80-1.70 (br s, 1H, OH), 1.26 (t, 3H, *J* = 7.2 Hz, H-4'), 0.89 (d, 3H, *J* = 7.2 Hz, 2-C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.60 (C-8), 173.70 (C-1'), 132.17 (<u>C</u>H=CH), 128.54 (<u>C</u>H=CH), 64.38 (C-1"), 60.28 (C-3'), 49.43 (<u>C</u>H), 43.25 (<u>C</u>H$_2$), 42.75 (<u>C</u>H), 38.76 (<u>C</u>H), 38.33 (<u>C</u>H), 32.76 (<u>C</u>H$_2$), 31.21 (<u>C</u>H), 17.76 (2-<u>C</u>H$_3$), 14.27 (C-4'); MS (EI) calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1507 (M^+, 14.3), 220.1102 (99), 192.1149 (100); Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.36; H, 8.59.

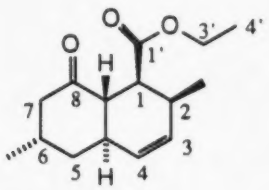
Procedure B. A modification of the method of Auerbach and Weinreb was employed.[169] A solution of methoxymethyl ketone **137** (11.3 mg, 36.2 μmol) in distilled EtOH (4 mL) and conc. HCl (1 drop) was heated to 63 °C for 1 h. The mixture was partitioned between Et_2O (30 mL) and H_2O (10 mL); the separated aqueous layer was treated with saturated $NaHCO_3$ (5 drops), and evaporated to dryness *in vacuo*. The residue was extracted with Et_2O (10 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 75% Et_2O in petroleum ether, R_f 0.25) to yield

the desired keto-ester **138** (9.46 mg, 98%) having the same physical and spectral data as shown above.



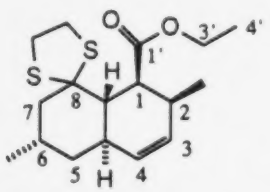
Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-6-[[[(methylthio)thiocarbonyl]oxy]methyl]naphthalen-8-one-1-carboxylate (139). **Procedure A.** The same procedure as for the preparation of ketone **137** was used. Thus, oxidation of alcohol **132** (1.14 g, 3.18 mmol) with pyridinium dichromate (1.79 g, 4.76 mmol) afforded **139** (0.908 g, 80%) as a colourless waxy solid after purification by flash chromatography (SiO_2; 40% Et_2O in pentane, R_f 0.30): mp 82-82.5 °C; $[\alpha]_D^{20}$ +160.5° (*c* 1.19, $CHCl_3$); IR (CH_2Cl_2) 2966 (m), 2927 (m), 2874 (m), 1733 (s), 1717 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (ddd, 1H, *J* = 9.8, 4.5, 2.6 Hz, C<u>H</u>=CH), 5.45 (ddd, 1H, *J* = 9.8, 1.6, 1.5 Hz, C<u>H</u>=CH), 4.52 (dd, 1H, *J* = 11.1, 7.9 Hz, 1 x H-1"), 4.45 (dd, 1H, *J* = 11.1, 6.9 Hz, 1 x H-1"), 4.22-4.09 (m, 2H, H-3'), 2.90-2.60 (m, 5H, H-1 & H-2 & H-4a & 1 x H-7 & H-8a), 2.73 (s, 3H, SC<u>H</u>$_3$), 2.38 (ddd, 1H, *J* = 13.7, 1.8, 1.8 Hz, 1 x H-7), 2.29 (ddm, 1H, *J* = 11.8, 11.8 Hz, H-6), 1.97 (dm, 1H, *J* = 14.1 Hz, H-5eq), 1.79 (ddd, 1H, *J* = 13.4, 13.4, 5.3 Hz, H-5ax), 1.26 (t, 3H, *J* = 7.2 Hz, H-4'), 0.89 (d, 3H, *J* = 7.2 Hz, 2-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.75 (S<u>C</u>SO), 209.03 (C-8), 173.51 (C-1'), 132.50 (<u>C</u>H=CH), 128.03 (<u>C</u>H=CH), 74.47 (C-1"), 60.30 (C-3'), 49.24 (<u>C</u>H), 42.99 (C-7), 42.63 (<u>C</u>H), 38.03 (C-6), 35.40 (<u>C</u>H), 32.92 (C-5), 31.15 (<u>C</u>H), 19.15 (S<u>C</u>H$_3$), 17.72 (2-<u>C</u>H$_3$), 14.26 (C-4'); MS (EI) calcd for $C_{17}H_{24}O_4S_2$ 356.1116, found 356.1110 (M^+, 18), 310.0696 (16), 202.0989 (100); Anal. Calcd for $C_{17}H_{24}O_4S_2$: C, 57.28; H, 6.79. Found: C, 56.98; H, 6.42.

Procedure B. The procedure B for the preparation of methyl xanthate **132** was used. Thus, treatment of primary alcohol **138** (21.6 mg, 81.2 μmol) with carbon disulfide (16.8 μL, 268 μmol) and methyl iodide (10.1 μL, 162 μmol) afforded **139** (22.8 mg, 79%) as a colourless waxy solid having the same physical and spectral data as those shown above.



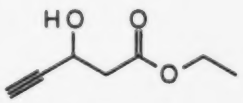
Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2,6-dimethylnaphthalen-8-one-1-carboxylate (140). The method of Barton *et al.* was followed.[127] A solution of tributyltin hydride (0.133 mL, 0.496 mmol) in dry cymene (2 mL) was slowly added to a solution of methyl xanthate **139** (22.1 mg, 0.062 mmol) in cymene (2 mL) at 150 °C over 1.25 h. The mixture was allowed to stir overnight at 150 °C. The solvent was removed *in vacuo* and the resultant oil purified by flash chromatography (SiO_2; 40% Et_2O in pentane, R_f 0.40) to yield **140** (9.75 mg, 63%) as a clear colourless solid: mp 34-35 °C; $[\alpha]_D^{20}$ +80.8° (*c* 0.13, $CHCl_3$); IR (CH_2Cl_2 cast) 3016 (w), 2960 (s), 2925 (s), 2874 (m), 2853 (m), 1736 (s), 1718 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (ddd, 1H, *J* = 9.8, 4.5, 2.8 Hz, C<u>H</u>=CH), 5.45 (ddd, 1H, *J* = 9.8, 1.6, 1.5 Hz, C<u>H</u>=CH), 4.23-4.09 (m, 2H, H-3'), 2.82 (dd, 1H, *J* = 11.5, 6.6 Hz, H-1), 2.75 (dd, 1H, *J* = 12.6, 6.6 Hz, H-8a), 2.70-2.50 (m, 3H, H-2 & H-7), 2.37-2.28 (m, 1H, H-6), 2.15 (ddd, 1H, *J* = 12.6, 1.9, 1.9 Hz, H-4a), 1.78 (ddd, 1H, *J* = 12.9, 12.9, 4.9 Hz, H-5ax), 1.69 (dp, 1H, *J* = 13.3, 1.8 Hz, H-5eq), 1.26 (t, 3H, *J* = 7.1 Hz, H-4'), 0.98 (d, 3H, *J* = 7.2 Hz, C<u>H</u>$_3$), 0.89 (d, 3H, *J* = 7.1 Hz, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.50 (C-8), 173.76 (C-1'), 132.15 (<u>C</u>H=CH), 128.87 (<u>C</u>H=CH), 60.22 (C-3'), 49.53 (<u>C</u>H), 48.11 (<u>C</u>H$_2$), 42.83 (<u>C</u>H), 38.01 (<u>C</u>H$_2$), 37.82

(CH), 31.35 (CH), 31.26 (CH), 19.39 (CH_3), 17.80 (CH_3), 14.28 (C-4'); MS (EI) calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1567 (M^+, 22), 204.1149 (76), 176.1198 (100); Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.71; H, 8.87.

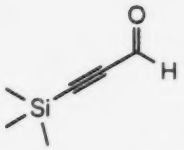


Ethyl (1*S*, 2*S*, 4a*R*, 6*S*, 8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-8-(dimethylenedithio)-2,6-dimethylnaphthalen-1-carboxylate (141). A modification of the procedure of Falck and coworkers was followed.[131] A solution of ketone **140** (0.244 g, 0.977 mmol) in dry CH_2Cl_2 (8 mL) was treated with 1,2-ethanedithiol (0.164 mL, 1.95 mmol) and boron trifluoride etherate (0.120 mL, 0.977 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1N NaOH (10 mL), 1N HCl (10 mL), H_2O (10 mL), and brine (10 mL). The solvent was removed *in vacuo* and the resultant oil was purified by flash chromatography (SiO_2; 10% Et_2O in pentane, R_f 0.22) to yield **141** (212 mg, 66%) as a clear colourless oil: $[\alpha]_D^{20}$ +84.3° (*c* 0.22, $CHCl_3$); IR (CH_2Cl_2 cast) 3027 (m), 2971 (s), 2958 (s), 2925 (s), 2876 (m), 2847 (m), 1730 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (br s, 2H, CH=CH), 4.11 (dm, 2H, *J* = 3.0 Hz, H-3'), 3.43-3.33 (m, 1H, 1 x SCH_2CH_2S), 3.33-3.28 (m, 1H, 1 x SCH_2CH_2S), 3.28-3.20 (m, 2H, 2 x SCH_2CH_2S), 3.10 (dd, 1H, *J* = 7.8, 6.2 Hz, H-1), 2.47 (br dq, 1H, *J* = 7.8, 7.4 Hz, H-2), 2.32-2.22 (m, 2H, H-7eq & H-7ax), 2.21 (dd, 1H, *J* = 10.9, 6.2 Hz, H-8a), 2.20-2.10 (m, 1H, H-6), 2.12-2.00 (br t, 1H, *J* = 12.3 Hz, H-4a), 1.75 (dm, 1H, *J* = 13.3 Hz, H-5eq), 1.62 (ddd, 1H, *J* = 12.7, 12.7, 5.3 Hz, H-5ax), 1.24 (t, 3H, *J* = 7.2 Hz, H-4'), 1.21 (d, 3H, *J* = 7.5 Hz, 6-CH_3), 1.10 (d, 3H, *J* = 7.4 Hz, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.20 (C-1'), 134.15

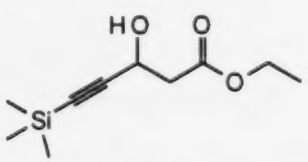
(CH=CH), 133.37 (CH=CH), 72.68 (C-8), 59.95 (C-3'), 54.22 (CH), 50.91 (CH_2), 49.74 (CH), 40.97 (CH_2), 38.50 (CH_2), 37.99 (CH_2), 33.71 (CH), 31.93 (CH), 29.50 (CH), 20.46 (CH_3), 17.64 (CH_3), 14.33 (OCH_2CH_3); MS (EI) calcd for $C_{17}H_{26}O_2S_2$ 326.1374, found 326.1369 (M^+, 60), 298.1050 (68), 219.0844 (27), 159.1168 (100); Anal. Calcd for $C_{17}H_{26}O_2S_2$: C, 62.54; H, 8.03. Found: C, 62.81; H, 8.34.



Ethyl (*R*,*S*)-3-Hydroxypent-4-ynoate (146).[11a] A mixture of 1M tetrabutylammonium fluoride in THF (108 mL, 108 mmol) and the unpurified silyl derivative **150** (11.0 g, 51.5 mmol) in THF (100 mL) was stirred at room temperature for 1 h, then diluted with Et_2O (300 mL). This mixture was washed with brine (2 x 200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford a brown oil, which was distilled at 45-50 °C (0.25 mm Hg) to give an orange oil (2.8 g). The oil was further purified by flash chromatography (SiO_2; 20% EtOAc in pentane, R_f 0.23) to yield **146** (2.6 g, 36%) as a clear oil: IR (neat) 3449 (br s), 3290 (s), 2984 (m), 2110 (w), 1732 (s), 1374 (s), 1277(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (tdd, 1H, *J* = 5.9, 6.2, 2.1 Hz, CH(OH)), 4.18 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 2.73 (d, 2 H, *J* = 5.9 Hz, CH_2COOEt), 3.31 (d, 1H, *J* = 6.2 Hz, CH(OH)), 2.46 (d, 1H, *J* = 2.1 Hz, C-H), 1.26 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.19 (COOEt), 82.98 (C), 73.22 (C), 61.08 (OCH_2CH_3), 58.52 (CH(OH)), 41.74 (CH_2COOEt), 14.13 (CH_2CH_3); MS (CI, NH_3) 160 (MNH_4^+, 100), 143 (MH^+, 50); Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.15; H, 7.39.

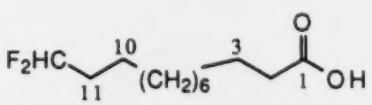


3-Trimethylsilyl-2-propynal (149).[11a] Ethyl bromide (42.0 g, 0.385 mol) was added to magnesium turnings (8.51 g, 0.350 mol) in THF (100 mL). When the formation of ethylmagnesium bromide was complete, a solution of (trimethylsilyl)acetylene (25.0 g, 0.254 mol) in THF (200 mL) was added over 50 min at 0 °C. The mixture was stirred at room temperature for 1 h, and then transferred by cannula to a solution of DMF (74.0 mL 0.955 mol) in Et_2O (100 mL) over 2 h at -28 °C. The mixture was warmed to room temperature and stirred for 1 h, and poured into ice cold 5% H_2SO_4 (500 mL). The aqueous solution was extracted with Et_2O (3 x 250 mL). A trace of hydroquinone was added to the combined organic extracts which were then concentrated to afford a brown oil. Distillation at 48-50 °C (H_2O aspirator) gave the aldehyde **149** (19.1 g, 59%): IR (neat) 2963 (m), 2859 (m), 2154 (m), 1681 (s), 1668 (s), 1254 (s), 1001 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1 H, C<u>H</u>O), 0.18 (s, 9 H, (C<u>H</u>$_3$)$_3$Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.65 (<u>C</u>HO), 102.88 (<u>C</u>), 102.14 (<u>C</u>), -1.00 ((<u>C</u>H$_3$)$_3$Si); MS (CI, NH_3) 144 (MNH_4^+, 3.5), 126 (18).



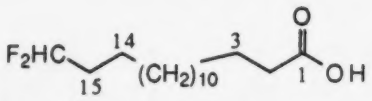
Ethyl (*R*,*S*)-5-Trimethylsilyl-3-hydroxypent-4-ynoate (150).[11a] EtOAc (14.4 mL, 147 mmol) was added to a solution of LHMDS [freshly made by the addition of 1.0 M *n*-BuLi (59.0 mL, 147 mmol) in hexanes to HMDS (31.0 g, 147.0 mmol) in THF (125 mL) at 0 °C] over 30 min at -78 °C. The solution was stirred for 30 min before addition of the aldehyde **149** (18.6 g, 147 mmol) at -78 °C. The reaction was continued

for 30 min at -78 °C, and the mixture was then allowed to warm to room temperature for a further 30 min. The mixture was poured into saturated aqueous ammonium chloride (1 L), and the resulting aqueous solution was extracted with EtOAc (3 x 300 mL). The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo* to give an orange liquid which could be used without further purification. Half of this material was distilled at 70°C (1 mm Hg) to yield **150** (11.0 g, 70%): IR (neat) 3450 (br m), 2984 (s), 2110 (w), 1740 (s), 1251 (s), 845 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (t, 1 H, J = 5.6 Hz, C<u>H</u>(OH)), 4.15 (q, 2 H, J = 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 3.15 (br s, 1H, O<u>H</u>), 2.69 (d, 2 H, J = 5.6 Hz, C<u>H</u>$_2$COOEt), 1.24 (t, 3 H, J = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 0.12 (s, 9 H, (C<u>H</u>$_3$)$_3$Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.16 (<u>C</u>OOEt), 104.55 (<u>C</u>), 89.71 (<u>C</u>), 60.91 (O<u>C</u>H$_2$CH$_3$), 59.08 (<u>C</u>H(OH)), 42.07 (<u>C</u>H$_2$COOEt), 14.13 (CH$_2$<u>C</u>H$_3$), -0.28 ((<u>C</u>H$_3$)$_3$Si); MS (CI, NH_3) 232 (MNH_4^+, 100), 215 (MH^+, 47); Anal. Calcd for $C_{10}H_{18}O_3Si$: C, 56.04; H, 8.46. Found: C, 56.44; H, 8.58.

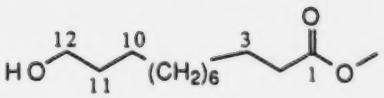


12,12-Difluorododecanoic Acid (151). A modification of the method of Seebach and coworkers was used.[104] A solution of methyl ester **159** (1.37 g, 5.50 mmol) in dry THF (20 mL) and 3M KOH (5 mL) was stirred overnight at room temperature. After 18 h, 50% of the THF was removed *in vacuo* and the cloudy solution was heated to 50 °C until it became homogeneous. The clear solution was diluted with H_2O (150 mL) and washed with pentane (2 x 20 mL). The aqueous layer was acidified to pH 5-6 with 1N HCl and extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **151** (1.26 g, 97%) as a white crystalline solid: mp 44-46 °C; IR (CH_2Cl_2 cast) 3300-2500 (br s), 2933 (s), 2915 (s), 2849 (s), 1704 (s), 1125 (m), 949 (m), 740 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 11.0 (br s, 1H, COO<u>H</u>), 5.77 (tt, 1H, J = 57.0, 4.5 Hz, H-12),

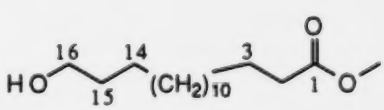
2.33 (t, 2H, J = 7.3 Hz, H-2), 1.94-1.73 (m, 2H, H-11), 1.73-1.55 (m, 2H, H-3), 1.48-1.22 (m, 14H, H-4 to H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.20 (C-1), 117.49 (t, J = 239 Hz, C-12), 34.09 (t, J = 20.6 Hz, C-11), 29.33 ($\underline{C}H_2$), 29.19 ($\underline{C}H_2$), 29.03 ($\underline{C}H_2$), 24.66 ($\underline{C}H_2$), 22.11 (t, J = 5.3 Hz, C-10); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -115.94 (dt, 2F, J = 57.0, 18.5 Hz, $C\underline{F}_2H$); MS (EI) calcd for $C_{12}H_{22}F_2O_2$ 236.1588, found 236.1588 (M^+, 29), 193.1039 (12), 176.1378 (23); Anal. Calcd for $C_{12}H_{22}F_2O_2$: C, 60.99; H, 9.38. Found: C, 60.96; H, 9.38.



16,16-Difluorohexadecanoic Acid (152). A modification of the procedure of Seebach and coworkers was followed.[104] A solution of methyl ester **160** (5.22 g, 17.0 mmol) in dry THF (4 mL), 3M KOH (30 mL) and H_2O (10 mL) was stirred at 50 °C overnight. The clear solution was diluted with H_2O (300 mL), acidified to pH 5-6 with 1N HCl, and extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*, to give a pale yellow crystalline solid. The solid was recrystallized from EtOH to yield **152** (4.45 g, 90%) as a white crystalline solid: mp 63-64 °C; IR (CH_2Cl_2 cast) 3200-2700 (br w), 2934 (s), 2915 (s), 2848 (s), 1701 (s), 1688 (m), 1125 (m), 982 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.0 (br s, 1H, COO$\underline{H}$), 5.79 (tt, 1H, J = 57.0, 4.6 Hz, H-16), 2.33 (t, 2H, J = 7.54 Hz, H-2), 1.87-1.73 (m, 2H, H-15), 1.66-1.57 (m, 2H, H-3), 1.48-1.38 (m, 2H, H-14), 1.38-1.20 (m, 20H, H-4 to H-13); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.31 (C-1), 117.49 (t, J = 239 Hz, C-16), 34.13 (t, J = 20.6 Hz, C-15), 29.62 ($\underline{C}H_2$), 29.46 ($\underline{C}H_2$), 29.40 ($\underline{C}H_2$), 29.28 ($\underline{C}H_2$), 29.10 ($\underline{C}H_2$), 24.72 ($\underline{C}H_2$), 22.10 (t, J = 5.4 Hz, C-14); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -115.92 (dt, 2F, J = 57.0, 18.5 Hz, $C\underline{F}_2H$); MS (EI) calcd for $C_{16}H_{30}F_2O_2$ 292.2214, found 292.2210 (M^+, 100); Anal. Calcd for $C_{16}H_{30}F_2O_2$: C, 65.72; H, 10.34. Found: C, 65.72 ; H, 10.00.

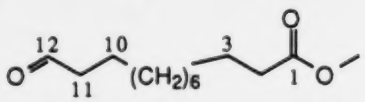


Methyl 12-Hydroxydodecanoate (155).[158] A solution of 12-hydroxydodecanoic acid (5.00 g, 23.0 mmol) in distilled MeOH (70 mL) and 6M HCl (2 mL) was heated to reflux with stirring overnight. The level of the solvent was reduced *in vacuo* and fresh MeOH was added. The solvent was removed again and this procedure was repeated two more times. After evaporation of the solvent *in vacuo*, the residue was partitioned between saturated aqueous $NaHCO_3$ (25 mL) and EtOAc (100 mL). The organic layer was washed again with saturated aqueous $NaHCO_3$ (25 mL). The combined aqueous layers were extracted with EtOAc (50 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give and pale yellow solid. This residue was purified by flash chromatography (SiO_2; 50 x 120 mm, 25% EtOAc in hexane, Rf 0.39) to yield **155** (5.19 g, 98%) as a white crystalline solid: mp 34-36 °C (lit.[158] mp 34-36 °C); IR (CH_2Cl_2 cast) 3314 (br s), 2932 (vs), 2851 (vs), 1744 (vs), 1471 (s), 1463 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H, $OC\underline{H}_3$), 3.61 (t, 2H, J = 6.6 Hz, H-12), 2.28 (t, 2H, J = 7.5 Hz, H-2), 1.65-1.50 (m, 5H, H-3 & H-11 & OH), 1.38-1.20 (m, 14H, H-4 - H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.39 (C-1), 63.03 (C-12), 51.44 ($O\underline{C}H_3$), 34.12 ($\underline{C}H_2$), 32.79 ($\underline{C}H_2$), 29.47 ($\underline{C}H_2$), 29.41 ($\underline{C}H_2$), 29.23 ($\underline{C}H_2$), 29.13 ($\underline{C}H_2$), 25.74 ($\underline{C}H_2$), 24.94 ($\underline{C}H_2$); MS (EI) calcd for $C_{13}H_{26}O_3$ 230.1882, found 231.1961 (MH^+, 1.5), 212.1780 (3.5), 200.1782 (90); Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.86; H, 11.30.

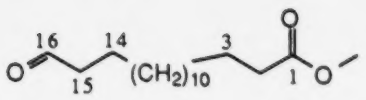


Methyl 16-Hydroxyhexadecanoate (156).[158] The same procedure as for the preparation of hydroxy ester **155** was used. 16-Hydroxyhexadecanoic acid (10.0 g, 36.7 mmol) in distilled MeOH (140 mL) and 6M HCl (4 mL) yielded **156** (10.5 g, 99%)

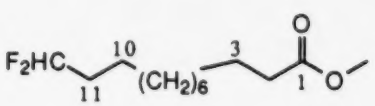
as a white crystalline solid: mp 55-57 °C (lit.[158] mp 55-57 °C); IR (CH_2Cl_2 cast) 3311 (br m), 2918 (s), 2849 (s), 1743 (s), 1472 (m), 1463 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H, $OC\underline{H}_3$), 3.62 (t, 2H, J = 6.7 Hz, H-16), 2.29 (t, 2H, J = 7.61 Hz, H-2), 1.65-1.53 (m, 4H, H-3 & H-15), 1.44 (br s, 1H, OH), 1.38-1.22 (m, 22H, H-4 to H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.42 (C-1), 63.13 (C-16), 51.47 ($O\underline{C}H_3$), 34.17 ($\underline{C}H_2$), 32.86 ($\underline{C}H_2$), 29.67 ($\underline{C}H_2$), 29.62 ($\underline{C}H_2$), 29.48 ($\underline{C}H_2$), 29.30 ($\underline{C}H_2$), 29.19 ($\underline{C}H_2$), 25.78 ($\underline{C}H_2$), 25.00 ($\underline{C}H_2$); MS (EI) calcd for $C_{17}H_{34}O_3$ 286.2508, found 287.2508 (MH^+, 1.3), 268.2409 (4.7); Anal. Calcd for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96. Found: C, 71.27; H, 11.87.



Methyl 12-Oxododecanoate (157).[158] A modification of the procedure of Nicolaou *et al.* was adopted.[92] A solution of alcohol **155** (4.00 g, 17.4 mmol) in dry CH_2Cl_2 (100 mL) was treated with activated 4Å molecular sieves and pyridinium chlorochromate (11.1 g, 29.5 mmol). The solution was stirred at room temperature for 2 h, then poured into Et_2O (1 L), and the mixture was filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2; 50 x 220 mm, 10% Et_2O in pentane, Rf 0.20) to yield **157** (2.87 g, 72%) as a clear liquid: IR (CH_2Cl_2 cast) 2932 (s), 2921 (s), 2852 (s), 2720 (w), 1744 (vs), 1471 (s), 1200 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, 1H, J = 1.8 Hz, H-12), 3.60 (s, 3H, $OC\underline{H}_3$), 2.35 (td, 2H, J = 7.4, 1.8 Hz, H-11), 2.23 (t, 2H, J = 7.7 Hz, H-2), 1.60-1.50 (m, 4H, H-3 & H-10), 1.28-1.19 (m, 12H, H-4 to H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.73 (C-12), 174.17 (C-1), 51.30 ($O\underline{C}H_3$), 43.79 ($\underline{C}H_2$), 33.97 ($\underline{C}H_2$), 29.23 ($\underline{C}H_2$), 29.11 ($\underline{C}H_2$), 29.04 ($\underline{C}H_2$), 29.01 ($\underline{C}H_2$), 24.83 ($\underline{C}H_2$), 21.97 ($\underline{C}H_2$); MS (EI) calcd for $C_{13}H_{24}O_3$ 228.1725, found 229.1807 (MH^+, 1.1), 213.1497 (6), 200.1781 (38).

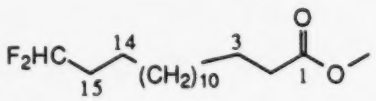


Methyl 16-Oxohexadecanoate (158).[170] A modification of the method of Furber and Mander was adopted.[129] Activated 4Å molecular sieves and pyridinium dichromate (19.7 g, 52.4 mmol) were added to a solution of alcohol **156** (10.0 g, 34.9 mmol) in dry CH_2Cl_2 (300 mL). The solution was stirred at room temperature for 3 h, then poured into Et_2O (300 mL) and filtered through flash silica gel (50 mm x 50 mm). The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2; 50 x 265 mm, 10% Et_2O in pentane, Rf 0.20) to yield **158** (6.64 g, 67%) as a white crystalline solid: mp 38-39 °C; IR (CH_2Cl_2 cast) 2917 (s), 2849 (s), 2720 (w), 1736 (s), 1720 (s), 1473 (m), 1463 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, 1H, J = 1.8 Hz, H-16), 3.63 (s, 3H, OCH_3), 2.39 (td, 2H, J = 7.34, 1.8 Hz, H-15), 2.27 (t, 2H, J = 7.5 Hz, H-2), 1.65-1.53 (m, 4H, H-3 & H-15), 1.38-1.22 (m, 20H, H-4 to H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.86 (C-16), 174.29 (C-1), 51.39 (OCH_3), 43.89 (CH_2), 34.09 (CH_2), 29.58 (CH_2), 29.55 (CH_2), 29.42 (CH_2), 29.33 (CH_2), 29.24 (CH_2), 29.14 (CH_2), 25.01 (CH_2), 22.07 (CH_2); MS (EI) calcd for $C_{17}H_{32}O_3$ 284.2351, found 285.2417 (MH+, 0.4), 256.2403 (13); Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.72; H, 11.08.



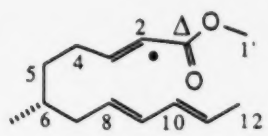
Methyl 12,12-Difluorododecanoate (159). The method of Middleton was followed.[159] A solution of the aldehyde **157** (1.77 g, 7.75 mmol) in dry CH_2Cl_2 (5 mL) was slowly added to a stirring solution of diethylaminosulfur trifluoride (DAST: 1.02 mL, 7.75 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The solution was stirred at room temperature for 1 h, then poured into H_2O (20 mL) and CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with H_2O (10 mL), 5% aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and

evaporated *in vacuo*. The pale yellow residue was distilled using a Kugelrohr apparatus to yield **159** (1.66 g, 86% yield) as a clear colourless oil: bp 144-146 °C (0.5 mm Hg); IR (CH_2Cl_2 cast) 2929 (vs), 2856 (vs), 1741 (vs), 1437 (m), 1123 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (tt, 1H, *J* = 57.0, 4.6 Hz, H-12), 3.66 (s, 3H, $OC\underline{H}_3$), 2.29 (t, 2H, *J* = 7.5 Hz, H-2), 1.88-1.73 (m, 2H, H-11), 1.66-1.57 (m, 2H, H-3), 1.48-1.38 (m, 2H, H-10), 1.38-1.20 (m, 12H, H-4 to H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.10 (C-1), 117.36 (t, *J* = 239 Hz, C-12), 51.20 ($O\underline{C}H_3$), 34.10 (t, *J* = 20.6 Hz, H-11), 29.26 ($\underline{C}H_2$), 29.13 ($\underline{C}H_2$), 29.04 ($\underline{C}H_2$), 28.96 ($\underline{C}H_2$), 24.85 ($\underline{C}H_2$), 22.02 (t, *J* = 5.2 Hz, C-10); ^{19}F NMR (376.5 MHz, $CDCl_3$ + $CFCl_3$) δ -115.91 (dt, 2F, *J* = 57.0, 18.5 Hz, $C\underline{F}_2H$); MS (EI) calcd for $C_{13}H_{24}F_2O_2$ 250.1744, found 250.1748 (M^+, 100), 219.1560 (84); Anal. Calcd for $C_{13}H_{24}F_2O_2$: C, 62.37; H, 9.66. Found: C, 62.52; H, 9.65.



Methyl 16,16-Difluorohexadecanoate (160). The same procedure as for the preparation of difluorinated methyl ester **159** was used. Thus, treatment of aldehyde **158** (6.12 g, 21.5 mmol) with DAST (2.84 mL, 21.5 mmol) afforded **160** (5.74 g, 87%) as a white crystalline solid after purification by flash chromatography (SiO_2; 50 x 225 mm, 2.5% Et_2O in pentane, R_f 0.20): mp 40-41 °C ; IR (CH_2Cl_2 cast) 2916 (s), 2849 (s), 1733 (s), 1473 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (tt, 1H, *J* = 57.0, 4.6 Hz, H-16), 3.65 (s, 3H, $OC\underline{H}_3$), 2.29 (t, 2H, *J* = 7.5 Hz, H-2), 1.87-1.73 (m, 2H, H-15), 1.66-1.57 (m, 2H, H-3), 1.48-1.38 (m, 2H, H-14), 1.38-1.20 (m, 20H, H-4 to H-13); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.03 (C-1), 117.53 (t, *J* = 239 Hz, C-16), 51.42 ($O\underline{C}H_3$), 34.10 (t, *J* = 19.9 Hz, C-15), 29.63 ($\underline{C}H_2$), 29.60 ($\underline{C}H_2$), 29.46 ($\underline{C}H_2$), 29.39 ($\underline{C}H_2$), 29.28 ($\underline{C}H_2$), 29.19 ($\underline{C}H_2$), 29.08 ($\underline{C}H_2$), 24.99 ($\underline{C}H_2$), 22.14 (t, *J* = 5.4 Hz, C-14); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -115.93 (dt, 2F, *J* = 57.0, 18.5 Hz, $C\underline{F}_2H$); MS (EI) calcd for $C_{17}H_{32}F_2O_2$ 306.2370, found 306.2373 (M^+, 36), 275.2188 (9); Anal.

Calcd for $C_{17}H_{32}F_2O_2$: C, 66.63; H, 10.53. Found: C, 66.77; H, 10.51.



• = ^{13}C Δ = $^{13/14}C$

30:70 Mixture of [1,2-$^{13}C_2$, 1-^{14}C] : [2-^{13}C, 1-^{14}C]-Methyl (6*R*)-*E*,*E*,*E*-6-Methyldodeca-2,8,10-trienoate (161). The same method as for the preparation of triene ethyl ester **83** was employed, except the $AgNO_3$-stained silica gel separation was not used; therefore, the product contained the 2*E*,8*E*,10*Z*-isomer (11% by ^1H NMR). Thus, aldehyde **74** (526 mg, 3.16 mmol), using a 30:70 mixture of [1,2-$^{13}C_2$, 1-^{14}C] : [2-^{13}C, 1-^{14}C]-(carbomethoxymethylene)triphenylphosphorane (isotopic purity 99% ^{13}C; 40 μCi) afforded **161** (506 mg, 75%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.10–6.90 (m, 1H, H-3), 6.06–5.93 (m, 2H, H-9 & H-10), 5.80 (ddm, 1H, *J* = 160.0, 15.6 Hz, H-2), 5.57 (dq, 1H, *J* = 14.2, 6.7 Hz, H-11), 5.50 (dt, 1H, *J* = 14.2, 7.0 Hz, H-8), 3.71 (s, 3H, OC$\underline{H}_3$), 2.30-2.10 (m, 2H, H-4), 2.10-2.00 (m, 1H, 1 x H-7), 2.00-1.87 (m, 1H, 1 x H-7), 1.72 (d, 3H, *J* = 6.7 Hz, H-12), 1.57-1.43 (m, 2H, 1 x H-5 & H-6), 1.34-1.16 (m, 1H, 1 x H-5), 0.87 (d, 3H, *J* = 6.5 Hz, 6-C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.20 (d, *J* = 72.0 Hz, C-1), 149.75 (d, *J* = 70.0 Hz, C-3), 131.91 (C-9), 131.62 (C-10), 129.82 (C-8), 127.11 (C-11), 120.80 (d & s, *J* = 72.0 Hz, C-2), 51.37 (O$\underline{C}H_3$), 39.91 (C-7), 34.69 (d, *J* = 3.0 Hz, C-4), 32.79 (C-6), 29.87 (C-5), 19.30 (6-$\underline{C}H_3$), 18.01 (C-12).

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